Inflammation and Repair. Acute inflammation. Chemical mediators and regulators of inflammation. Chronic and granulomatous inflammation, healing. Chronic inflammation; granulomatous inflammation; tuberculosis, sarcoidosis, etc. wound healing and repair; bone healing.

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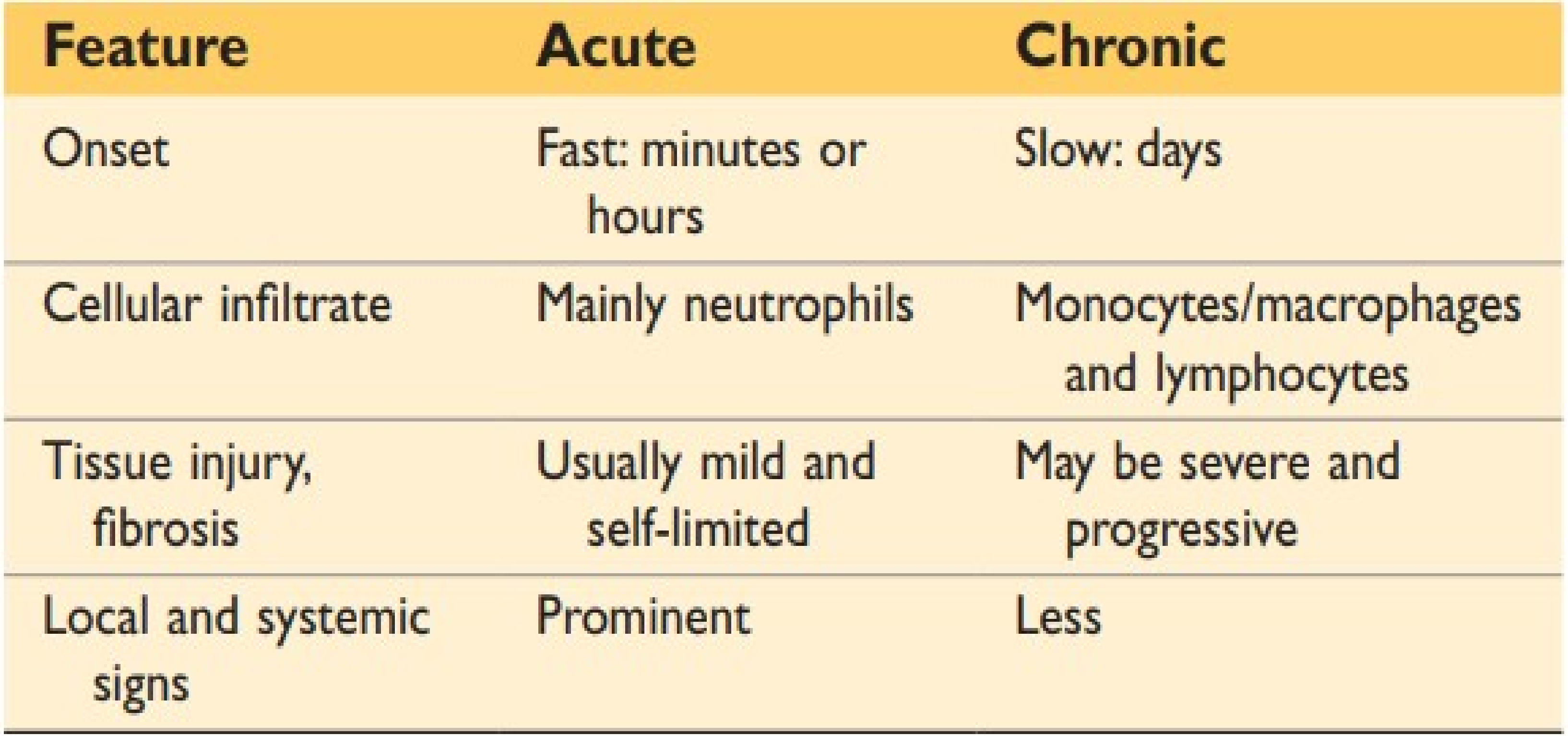
- Inflammation is a response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites where they are needed, to eliminate the offending agents.
- The process of inflammation delivers leukocytes and proteins to foreign invaders, such as microbes, and to damaged or necrotic tissues, and it activates the recruited cells and molecules, which then function to eliminate the harmful or unwanted substances.

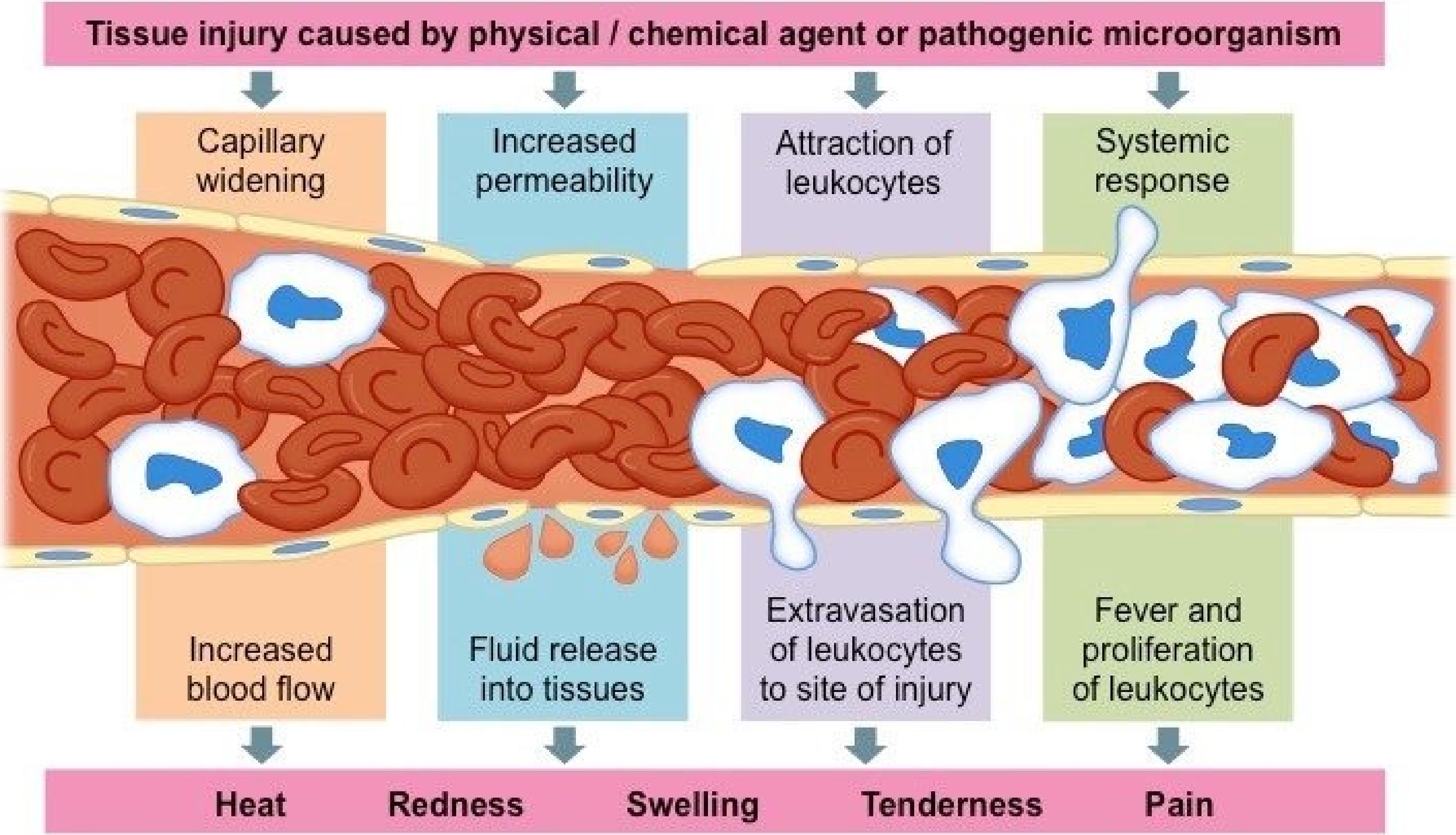
- Inflammation may be of two types, acute and chronic.



Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

- Inflammation is induced by chemical mediators that are produced by host cells in response to injurious stimuli.
- When a microbe enters a tissue or the tissue is injured, the presence of the infection or damage is sensed by resident cells, including macrophages, dendritic cells, mast cells, and other cell types.
- The external manifestations of inflammation, often called its cardinal signs, are heat (calor in Latin), redness (rubor), swelling (tumor), pain (dolor), and loss of function (functio laesa).

Cardinal signs		
Rubor and calor	Redness and warmth. Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow.	Histamine, prostaglandins, bradykinin, NO.
Tumor	Swelling. Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure.	Endothelial contraction: leukotrienes (C_4, D_4, E_4), histamine, serotonin.
Dolor	Pain. Sensitization of sensory nerve endings.	Bradykinin, PGE_2, histamine.
Functio laesa	Loss of function. Inflammation impairs function (eg, inability to make fist due to hand cellulitis).	



Tissue injury caused by physical / chemical agent or pathogenic microorganism

Capillary widening

Increased blood flow

Increased permeability

Fluid release into tissues

Attraction of leukocytes

Extravasation of leukocytes to site of injury

Systemic response

Fever and proliferation of leukocytes

Heat **Redness** **Swelling** **Tenderness** **Pain**

Etiologies

- Microbial infections: bacterial, viral, fungal, etc.
- Physical agents: burns, trauma--like cuts, radiation
- Chemicals: drugs, toxins, or caustic substances like battery acid.
- Immunologic reactions: rheumatoid arthritis.

RECOGNITION OF MICROBES AND DAMAGED CELLS

- ➔ The first step in inflammatory responses is the recognition of microbes and necrotic cells by cellular receptors and circulating proteins.

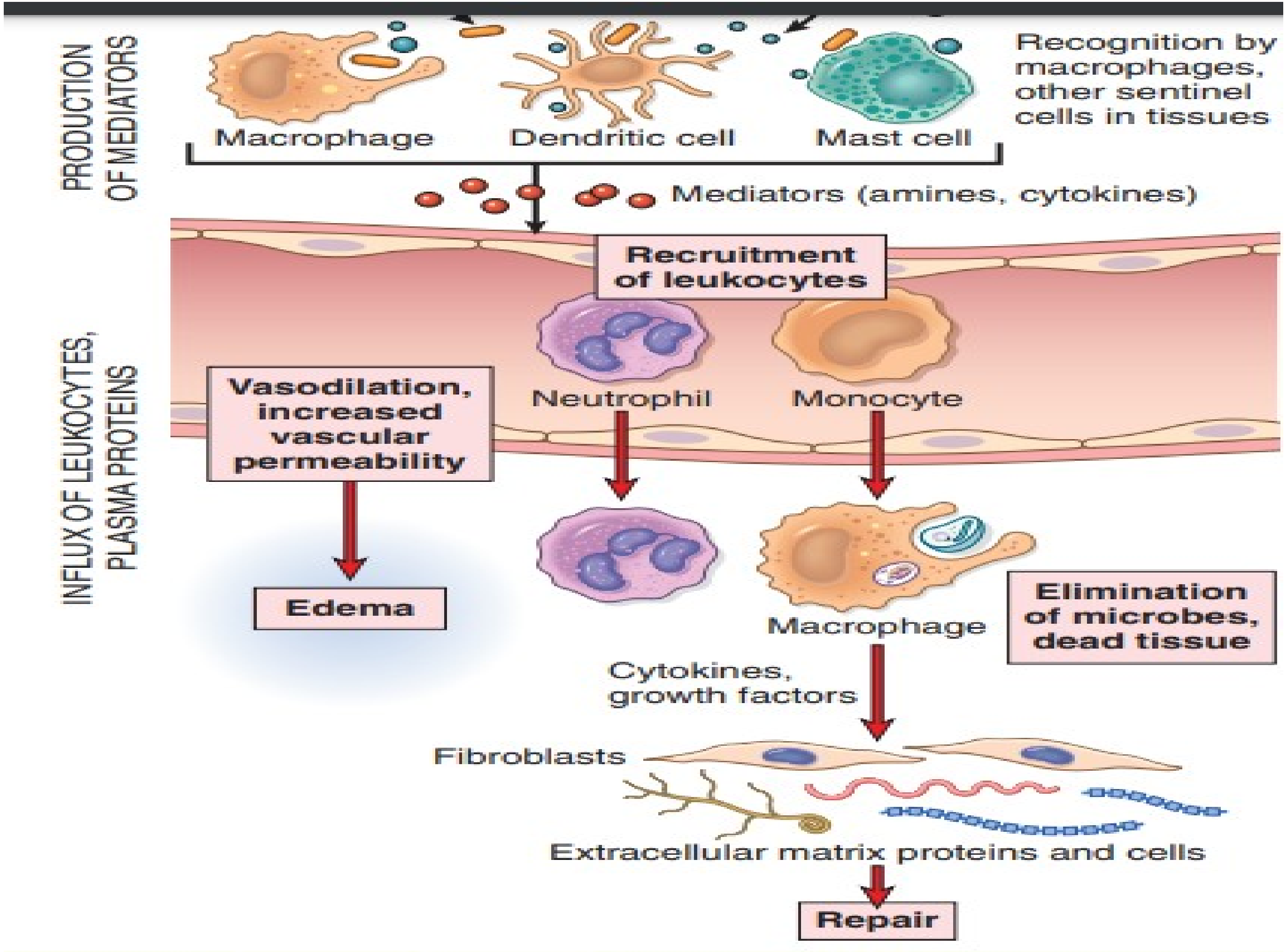
Cellular receptors for microbes-The best defined of these receptors belong to the family of Toll-like receptors (TLRs), which are named for the founding member, Toll, a gene that was discovered in Drosophila.

TLRs are located in plasma membranes and endosomes, so they are able to detect extracellular and ingested microbes.

Sensors of cell damage-All cells have cytosolic receptors that recognize molecules that are liberated or altered as a consequence of cell damage, and are hence appropriately called damage-associated molecular patterns (DAMPs).

The receptors activate a multiprotein cytosolic complex called the inflammasome, which induces the production of the cytokine interleukin-1 (IL-1).

Circulating proteins-The complement system reacts against microbes and produces mediators of inflammation.


PRODUCTION OF MEDIATORS
Macrophage
Dendritic cell
Mast cell
Recognition by macrophages, other sentinel cells in tissues
Mediators (amines, cytokines)
INFLUX OF LEUKOCYTES, PLASMA PROTEINS
Recruitment of leukocytes
Vasodilation, increased vascular permeability
Neutrophil
Monocyte
Edema
Macrophage
Elimination of microbes, dead tissue
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

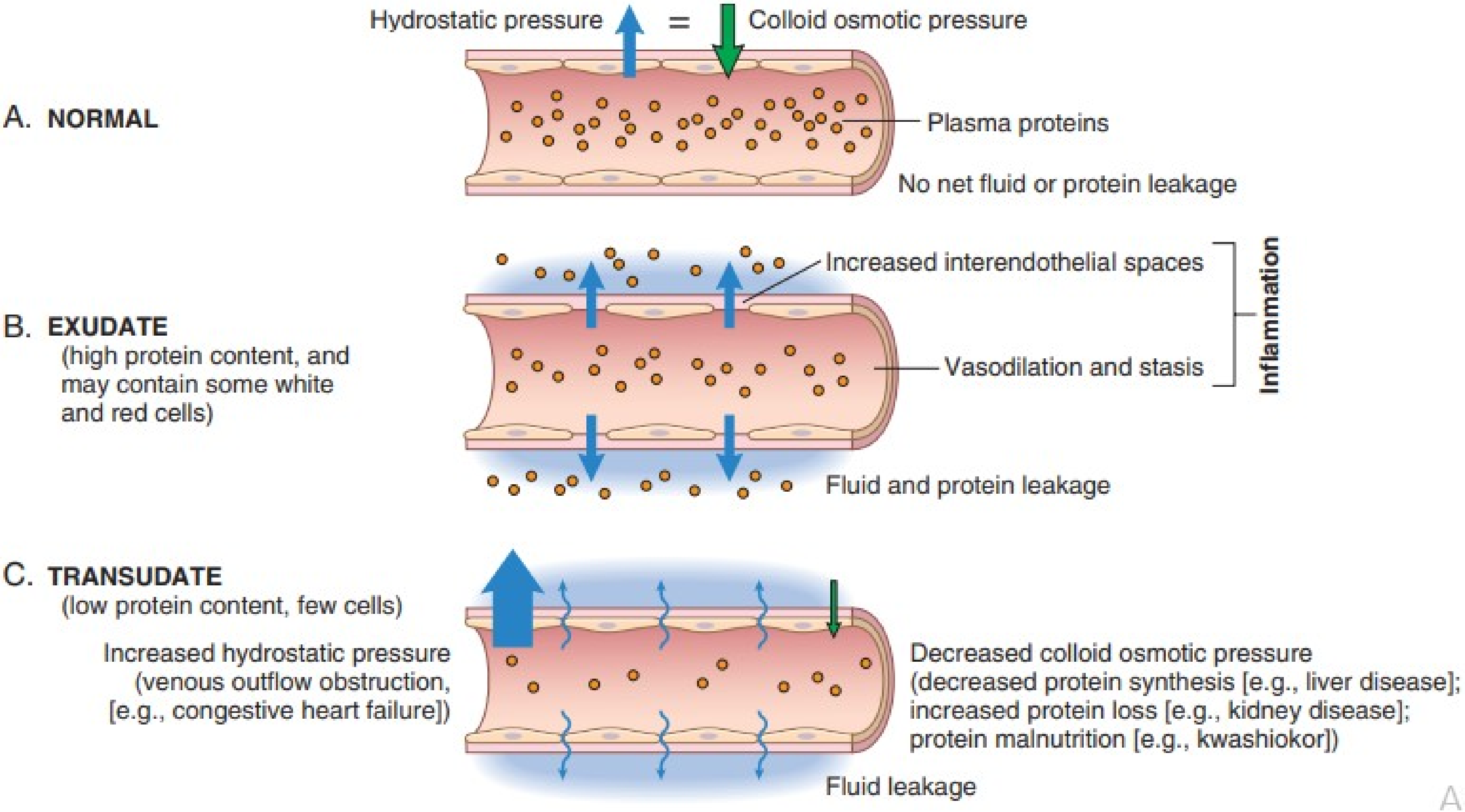
ACUTE INFLAMMATION

Acute inflammation has three major components:

(1) ***dilation of small vessels***, leading to an increase in blood flow

(2) ***increased permeability*** of the microvasculature, enabling plasma proteins and leukocytes to leave the circulation.

(3) ***emigration of the leukocytes*** from the microcirculation.



Hydrostatic pressure = Colloid osmotic pressure

A. **NORMAL**

Plasma proteins

No net fluid or protein leakage

B. **EXUDATE**
(high protein content, and may contain some white and red cells)

Increased interendothelial spaces

Vasodilation and stasis

Inflammation

Fluid and protein leakage

C. **TRANSUDATE**
(low protein content, few cells)

Increased hydrostatic pressure (venous outflow obstruction, [e.g., congestive heart failure])

Decreased colloid osmotic pressure (decreased protein synthesis [e.g., liver disease]; increased protein loss [e.g., kidney disease]; protein malnutrition [e.g., kwashiokor])

Fluid leakage

Activ

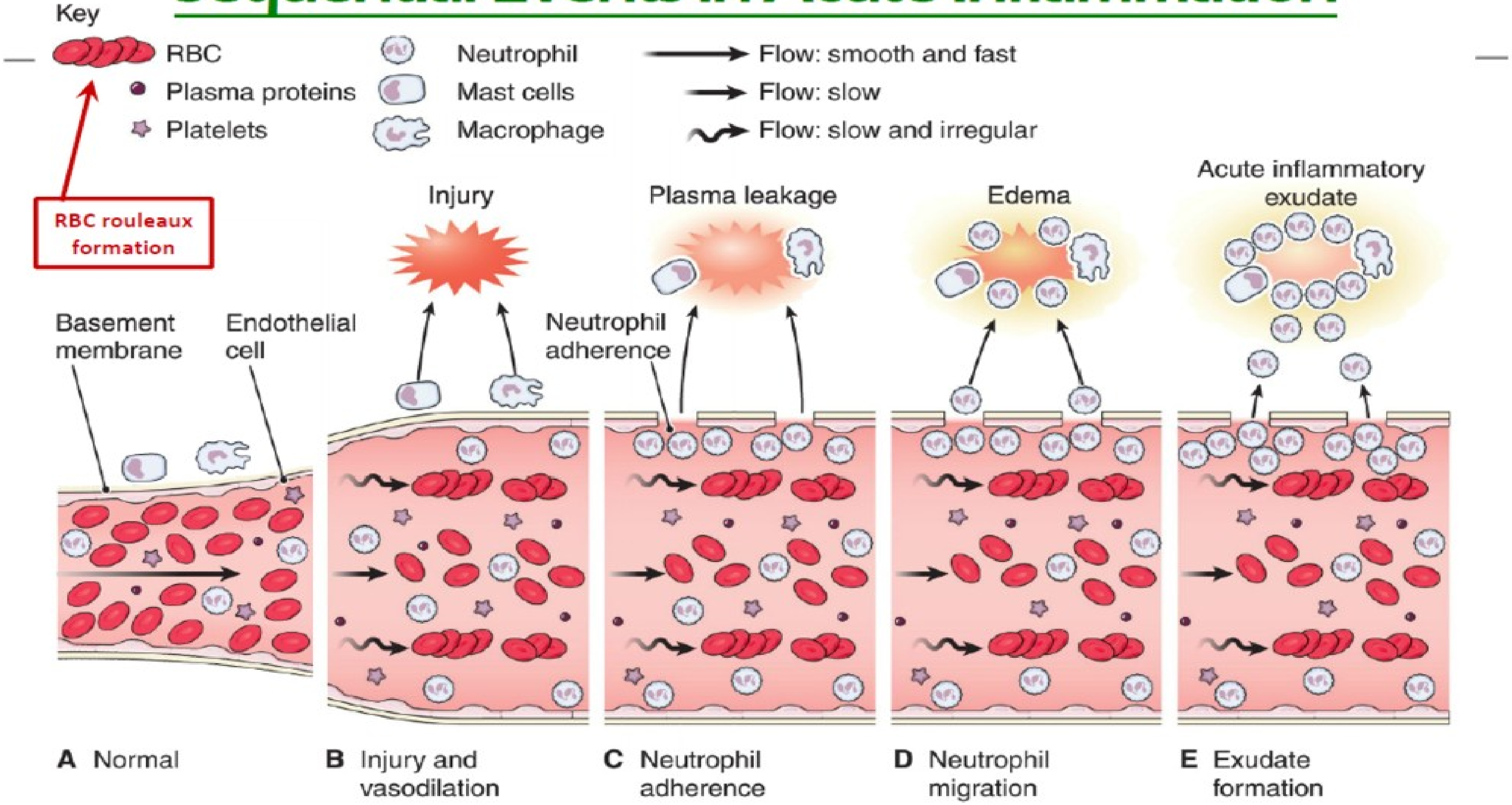
- **Vasodilation** is induced by inflammatory mediators such as histamine and is the cause of erythema and stasis of blood flow.

- **Increased vascular permeability** is induced by histamine, kinins, and other mediators that produce gaps between endothelial cells, by direct or leukocyte-induced endothelial injury, and by increased passage of fluids through the endothelium.

- **Increased vascular permeability** allows plasma proteins and leukocytes, the mediators of host defense, to enter sites of infection or tissue damage

- Fluid leak from blood vessels (exudation) results in ***edema***

Sequential Events in Acute Inflammation



The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis, namely, neutrophils and macrophages. Neutrophils are produced in the bone marrow and rapidly recruited to sites of inflammation. Macrophages are slower responders.

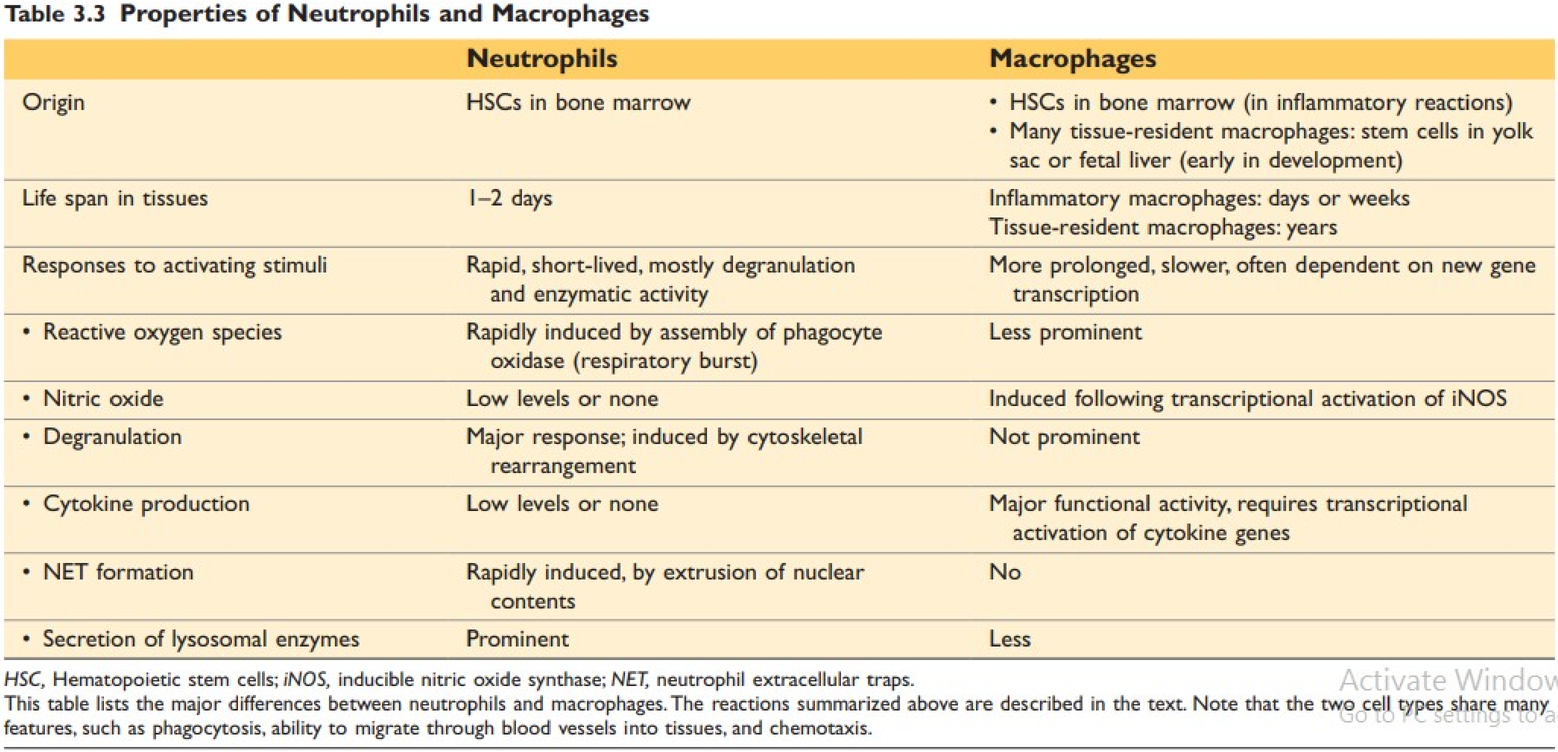


Table 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	**Macrophages**
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS,* inducible nitric oxide synthase; *NET,* neutrophil extracellular traps.

This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

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- The attachment of leukocytes to endothelial cells is mediated by complementary adhesion molecules on the two cell types whose expression is enhanced by cytokines. Cytokines are secreted by cells in tissues in response to microbes and other injurious agents, thus ensuring that leukocytes are recruited to the tissues where these stimuli are present.
- *Selectins mediate the initial weak interactions between leukocytes and endothelium.*

- *Selectins are receptors expressed on leukocytes and endothelium that contain an extracellular domain that binds sugars*

- Firm adhesion of leukocytes to endothelium is mediated by a family of leukocyte surface proteins called integrins.
- ***Integrins*** are transmembrane two-chain glycoproteins that mediate the adhesion of leukocytes to endothelium and of various cells to the extracellular matrix
- They are normally expressed on **leukocyte plasma membranes** in a low-affinity form and do not adhere to their specific ligands until the leukocytes are activated by chemokines.

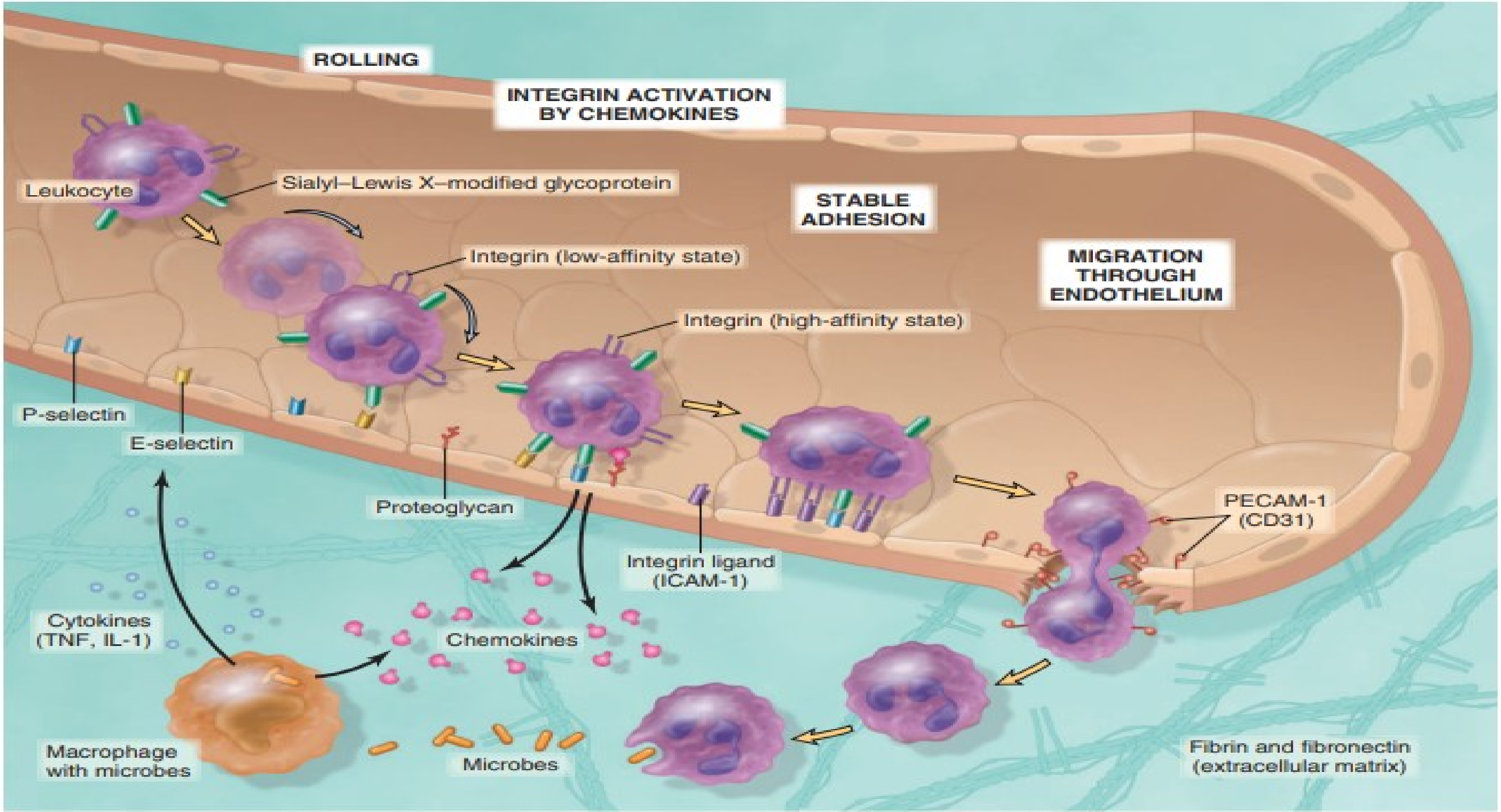

ROLLING
INTEGRIN ACTIVATION BY CHEMOKINES
STABLE ADHESION
MIGRATION THROUGH ENDOTHELIUM
Leukocyte
Sialyl–Lewis X–modified glycoprotein
Integrin (low-affinity state)
Integrin (high-affinity state)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
PECAM-1 (CD31)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

Fig. 3.4 The multistep process of leukocyte migration through blood vessels, shown here for neutrophils. The leukocytes first roll, then become activated and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and move toward chemoattractants emanating from

Recognition of microbes or dead cells induces several responses in leukocytes that are collectively called leukocyte a

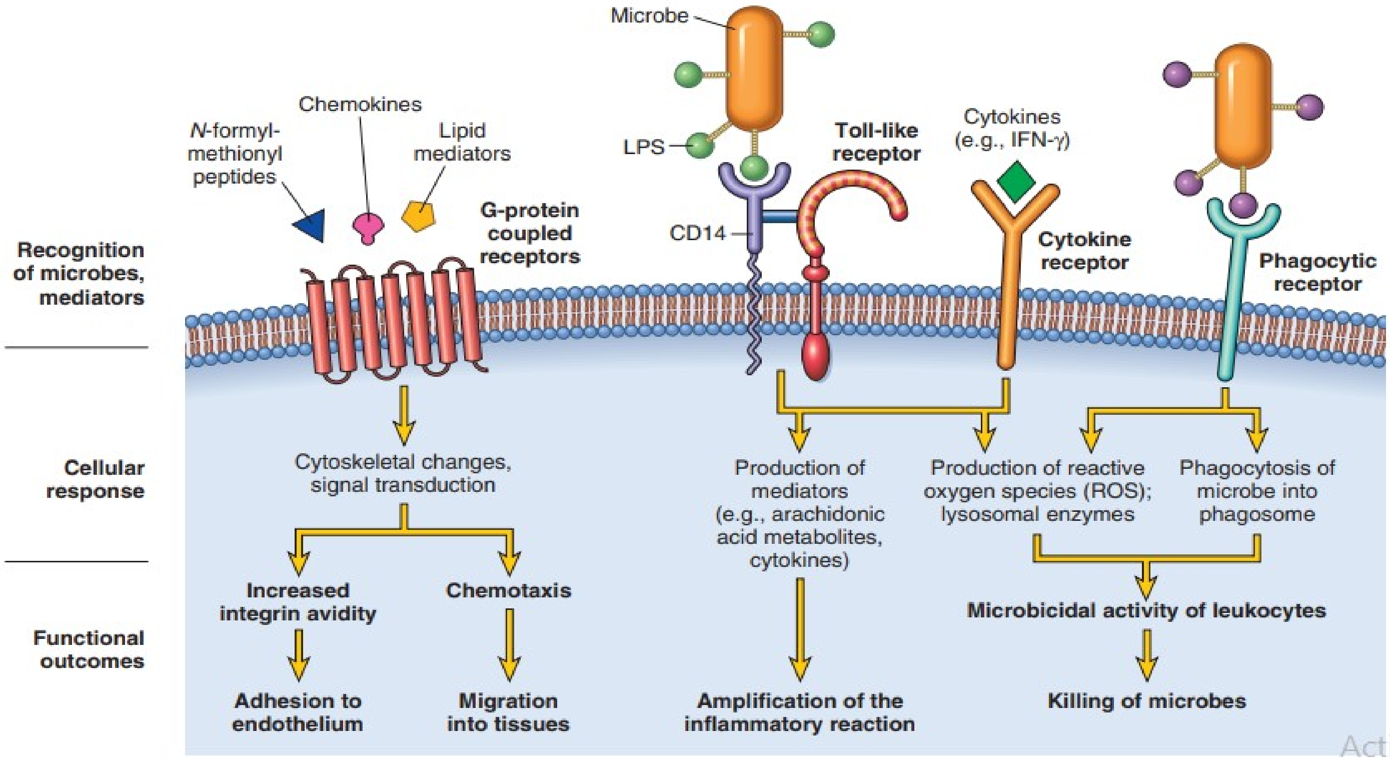
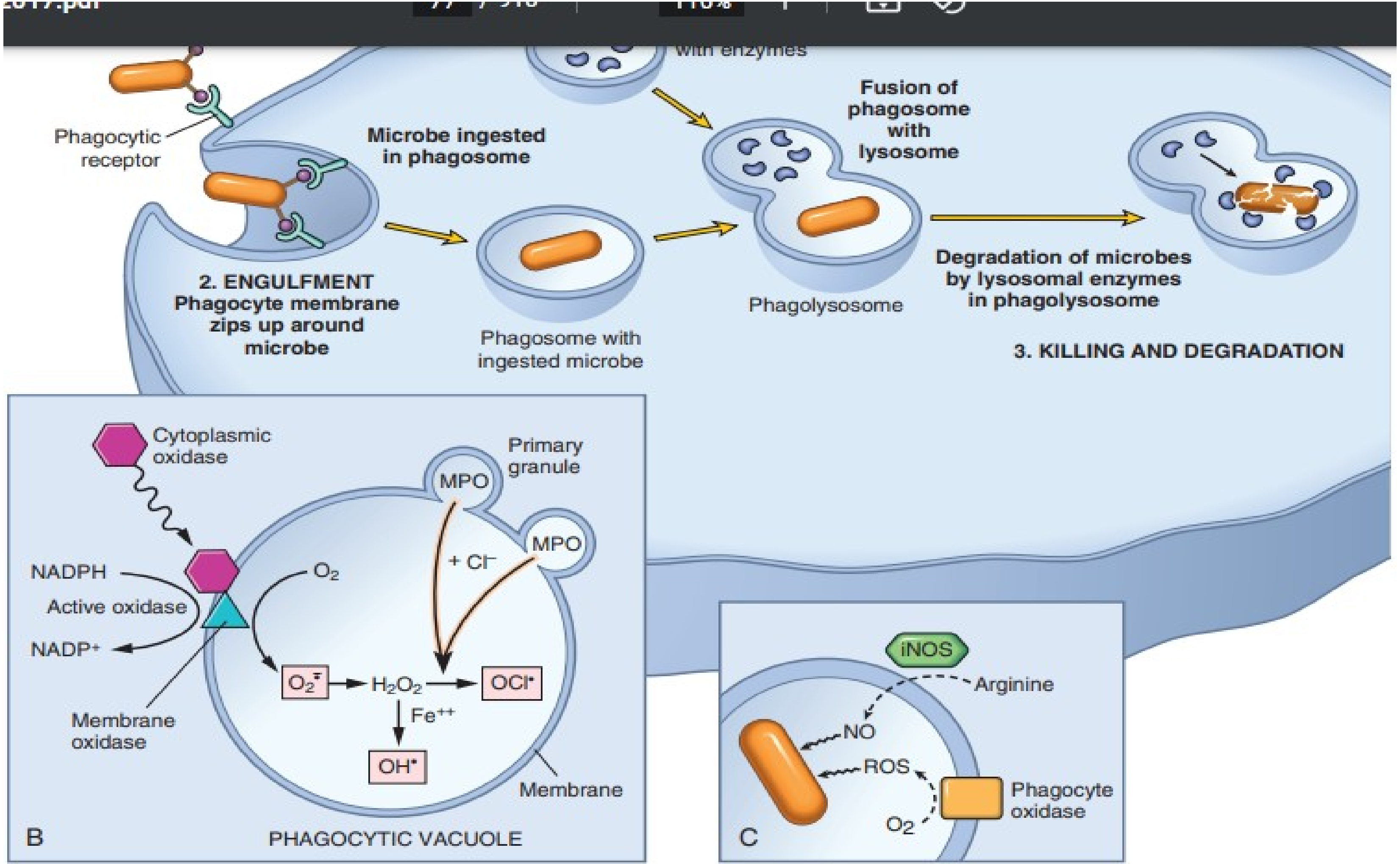

Microbe
LPS
CD14
Toll-like receptor
Cytokines (e.g., IFN-γ)
Cytokine receptor
Phagocytic receptor
Chemokines
N-formyl-methionyl peptides
Lipid mediators
G-protein coupled receptors
Recognition of microbes, mediators
Cellular response
Functional outcomes
Cytoskeletal changes, signal transduction
Production of mediators (e.g., arachidonic acid metabolites, cytokines)
Production of reactive oxygen species (ROS); lysosomal enzymes
Phagocytosis of microbe into phagosome
Increased integrin avidity
Chemotaxis
Microbicidal activity of leukocytes
Adhesion to endothelium
Migration into tissues
Amplification of the inflammatory reaction
Killing of microbes

Fig. 3.6 Leukocyte activation. Various types of leukocyte cell surface receptors recognize different agonists. Once stimulated, the receptors initiate responses that mediate leukocyte functions. Only some receptors are depicted (see text for details). LPS first binds to a circulating LPS-binding protein (not shown). *IFN-γ,* Interferon-γ; *LPS,* lipopolysaccharide.

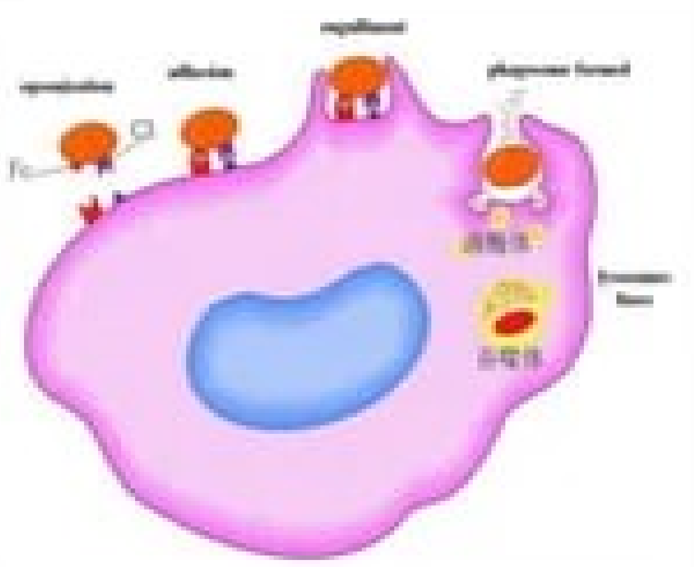

with enzymes
Phagocytic receptor
Microbe ingested in phagosome
Fusion of phagosome with lysosome
2. ENGULFMENT
Phagocyte membrane zips up around microbe
Phagosome with ingested microbe
Phagolysosome
Degradation of microbes by lysosomal enzymes in phagolysosome
3. KILLING AND DEGRADATION
Cytoplasmic oxidase
Primary granule
MPO
MPO
NADPH
Active oxidase
NADP+
O_2
+ Cl⁻
$O_2^{\bar{\cdot}}$
H_2O_2
OCl•
Fe++
OH•
Membrane oxidase
Membrane
B
PHAGOCYTIC VACUOLE
iNOS
Arginine
NO
ROS
Phagocyte oxidase
O_2
C

Phagocytosis

- **Phagocytosis is defined as the process of engulfment of solid particulate material by the cells (cell-eating).**

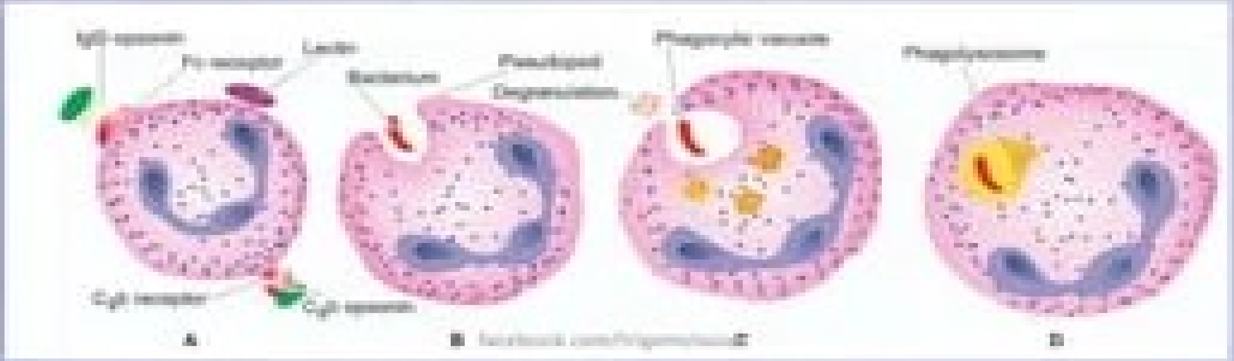
- **The cells performing this function are called *phagocytes*.**

- **Degranulation and the oxidative burst destroy the engulfed particle**



PHAGOCYTOSIS

- The microbe undergoes the process of phagocytosis in following 3 steps :
  - Recognition and attachment
  - Engulfment
  - Killing and degradation



Engulfment

- Formation of cytoplasmic pseudopods by the phagocytes around the bacteria.
- The bacteria is endocytosed and is contained in a vesicle thus forming a phagosome
- The phagosome fuses with nearby lysosome to form phagolysosome.

Meadiators of inflammation

- Mediators are the substances that initiate and regulate inflammatory reactions.
- These are: cell derived or plasma protein derived
- vasoactive amines,
- lipid products,
- cytokines,
- products of complement activation

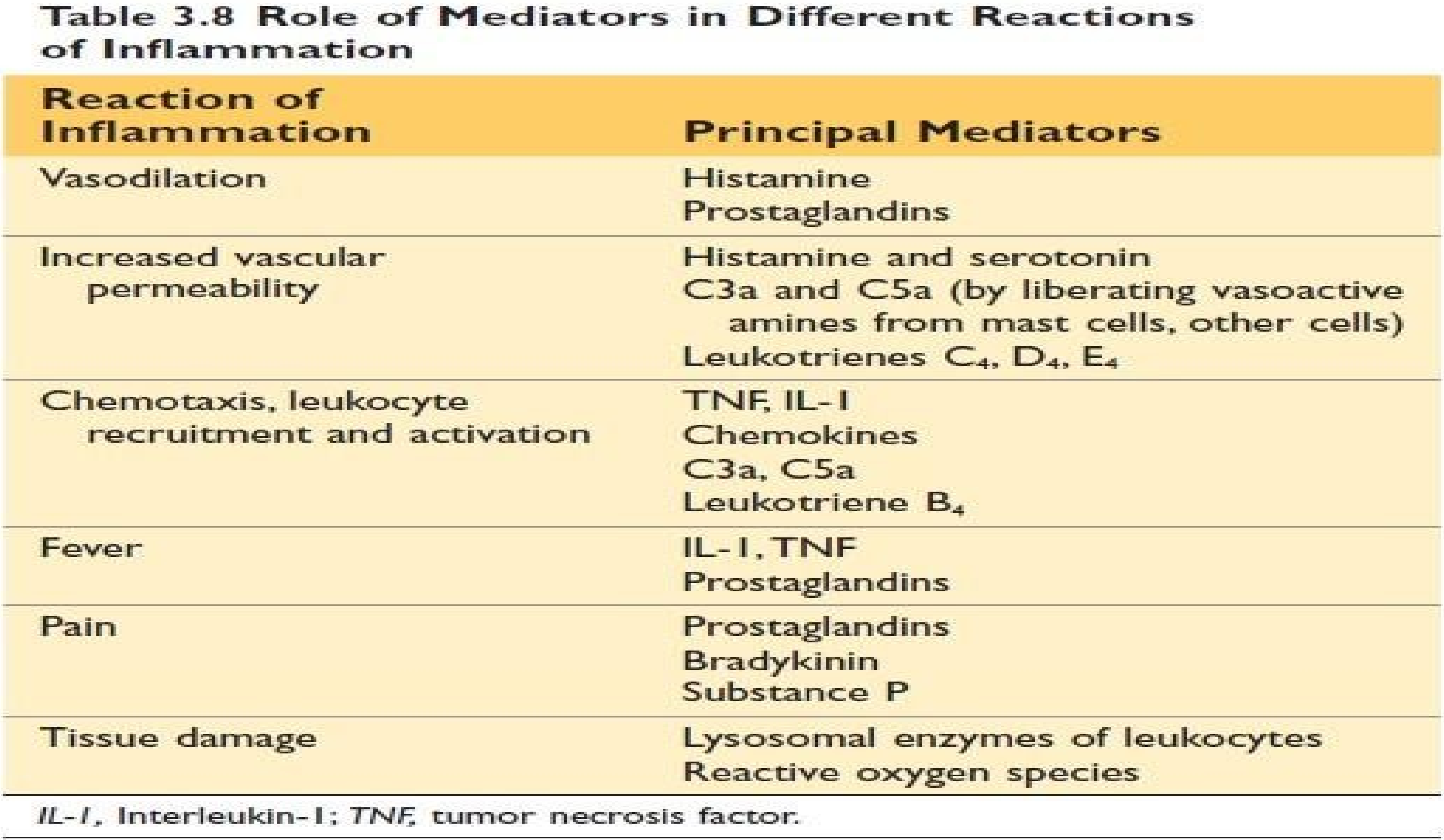


Table 3.8 Role of Mediators in Different Reactions of Inflammation

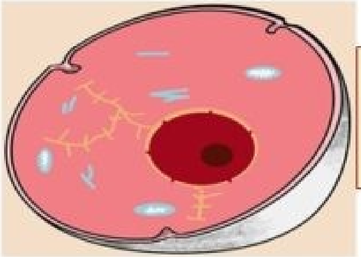
Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin Substance P
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

IL-1, Interleukin-1; *TNF*, tumor necrosis factor.

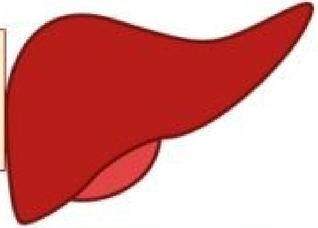
Table 3.7 Cytokines in Inflammation

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

IFN-γ, Interferon-γ; *IL,* interleukin; *NK,* natural killer; *TNF,* tumor necrosis factor.



CHEMICAL MEDIATORS OF INFLAMMATION



Cell - Derived

Preformed

- Histamine
- Serotonin

Synthesised de novo

- Arachidonic acid metabolites
- Platelet activating factor
- NO
- Reactive oxygen species
- Cytokines
- Chemokines

Plasma - Derived

Compliment activation

- C3a
- C3b
- C5a

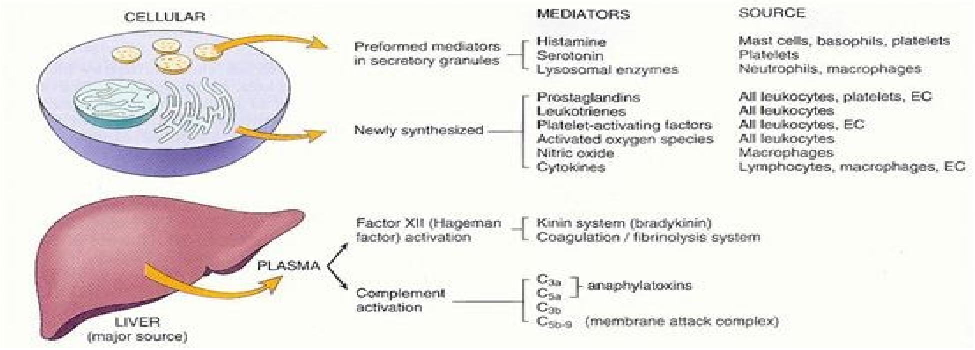
Factor XII activation

- Coagulation system
- Kinin system

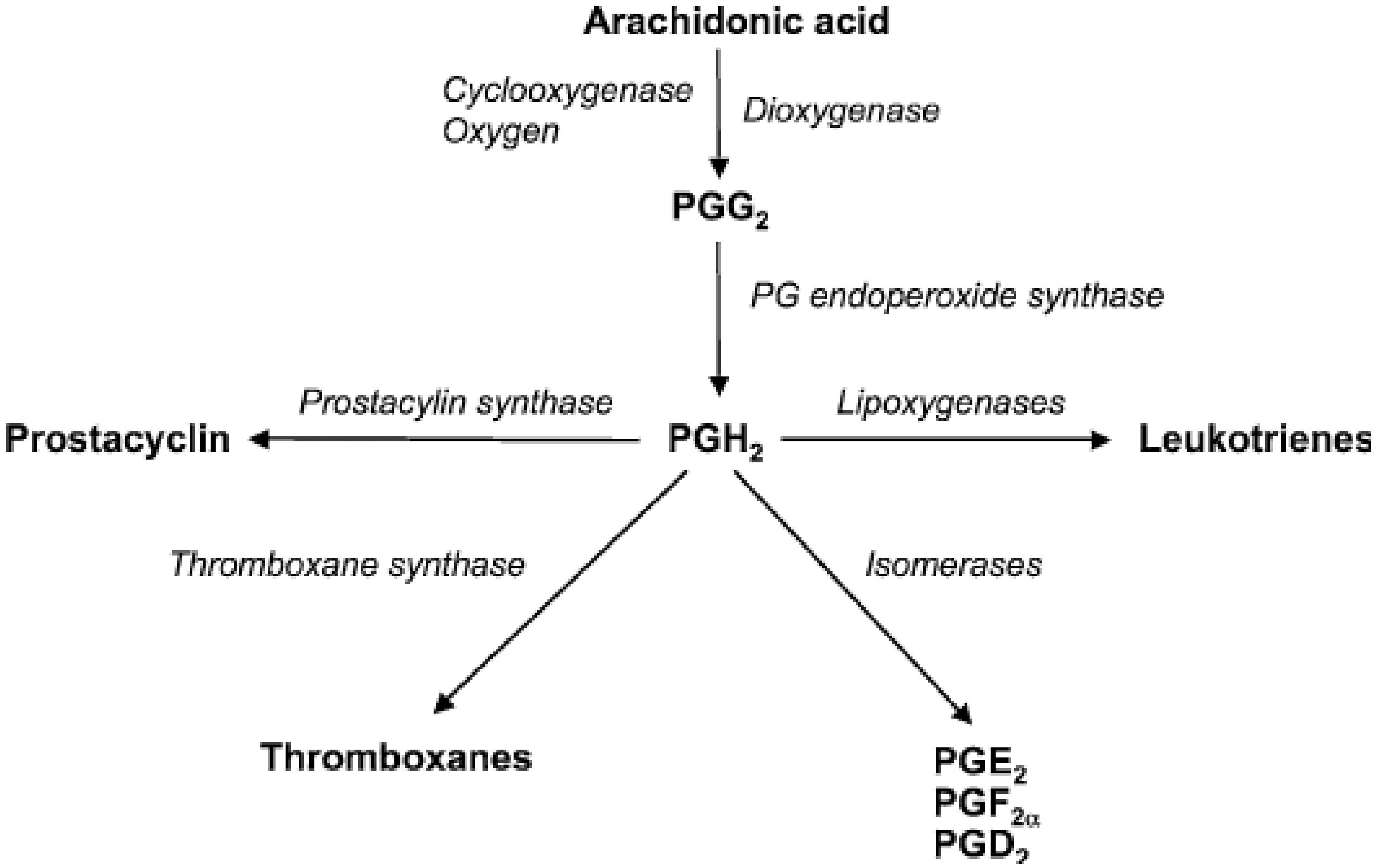
@VijayPatho

CHEMICAL MEDIATORS

- Vasodilation
  - Prostaglandins, Nitric Oxide
- Increased Vascular Permeability
  - Vasoactive amines (histamine, serotonin), C3a and C5a, Bradykinin, Leukotrienes, PAF,
- Chemotaxic Leukocyte Activation
  - C5a, LTB_4, Chemokines

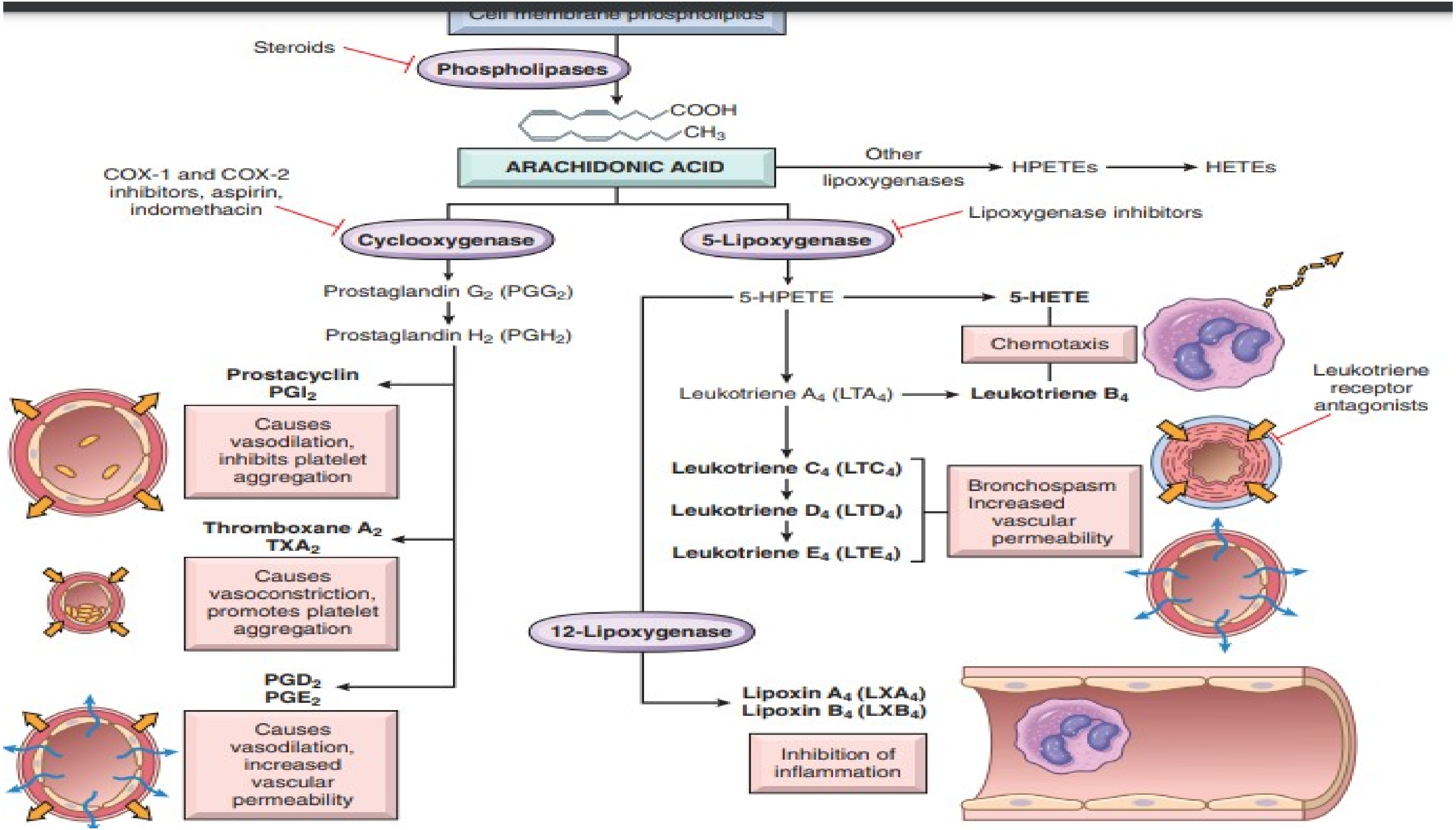


	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	
Complement activation	C_{3a} anaphylatoxins	
	C_{5a} anaphylatoxins	
	C_{3b}	
	C_{5b-9} (membrane attack complex)	


Arachidonic acid
Cyclooxygenase
Oxygen
Dioxygenase
PGG$_2$
PG endoperoxide synthase
Prostacylin synthase
Lipoxygenases
Prostacyclin
PGH$_2$
Leukotrienes
Thromboxane synthase
Isomerases
Thromboxanes
PGE$_2$
PGF$_{2\alpha}$
PGD$_2$

ROLE IN INFLAMMATION

- Arachidonic acid metabolites are important in inflammation. Evidence supporting this conclusion includes that:
- 1. exogenous PGs and LTs can promote inflammation.
- 2. PGs and L T s are found in inflammatory exudates.
- 3. drugs which inhibit cyclooxygenase, reduce inflammation.



Cell membrane phospholipids

Steroids

Phospholipases

COOH

CH_3

ARACHIDONIC ACID

Other lipoxygenases

HPETEs

HETEs

COX-1 and COX-2 inhibitors, aspirin, indomethacin

Cyclooxygenase

Lipoxygenase inhibitors

5-Lipoxygenase

Prostaglandin G_2 (PGG_2)

Prostaglandin H_2 (PGH_2)

Prostacyclin
PGI_2

Causes vasodilation, inhibits platelet aggregation

Thromboxane A_2
TXA_2

Causes vasoconstriction, promotes platelet aggregation

PGD_2
PGE_2

Causes vasodilation, increased vascular permeability

5-HPETE

5-HETE

Chemotaxis

Leukotriene A_4 (LTA_4)

Leukotriene B_4

Leukotriene receptor antagonists

Leukotriene C_4 (LTC_4)

Leukotriene D_4 (LTD_4)

Leukotriene E_4 (LTE_4)

Bronchospasm
Increased vascular permeability

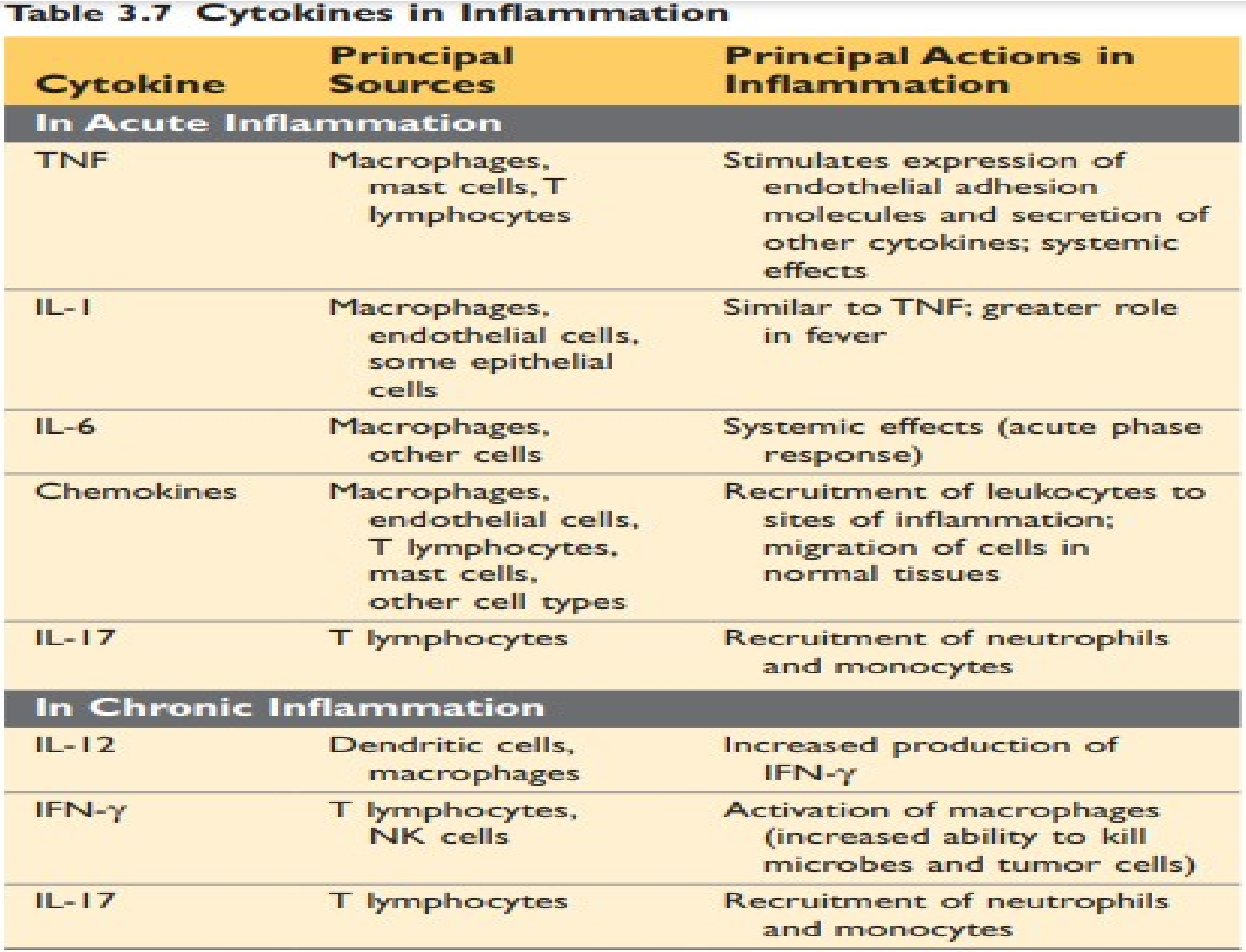
12-Lipoxygenase

Lipoxin A_4 (LXA_4)
Lipoxin B_4 (LXB_4)

Inhibition of inflammation

Table 3.6 Principal Actions of Arachidonic Acid Metabolites in Inflammation

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4



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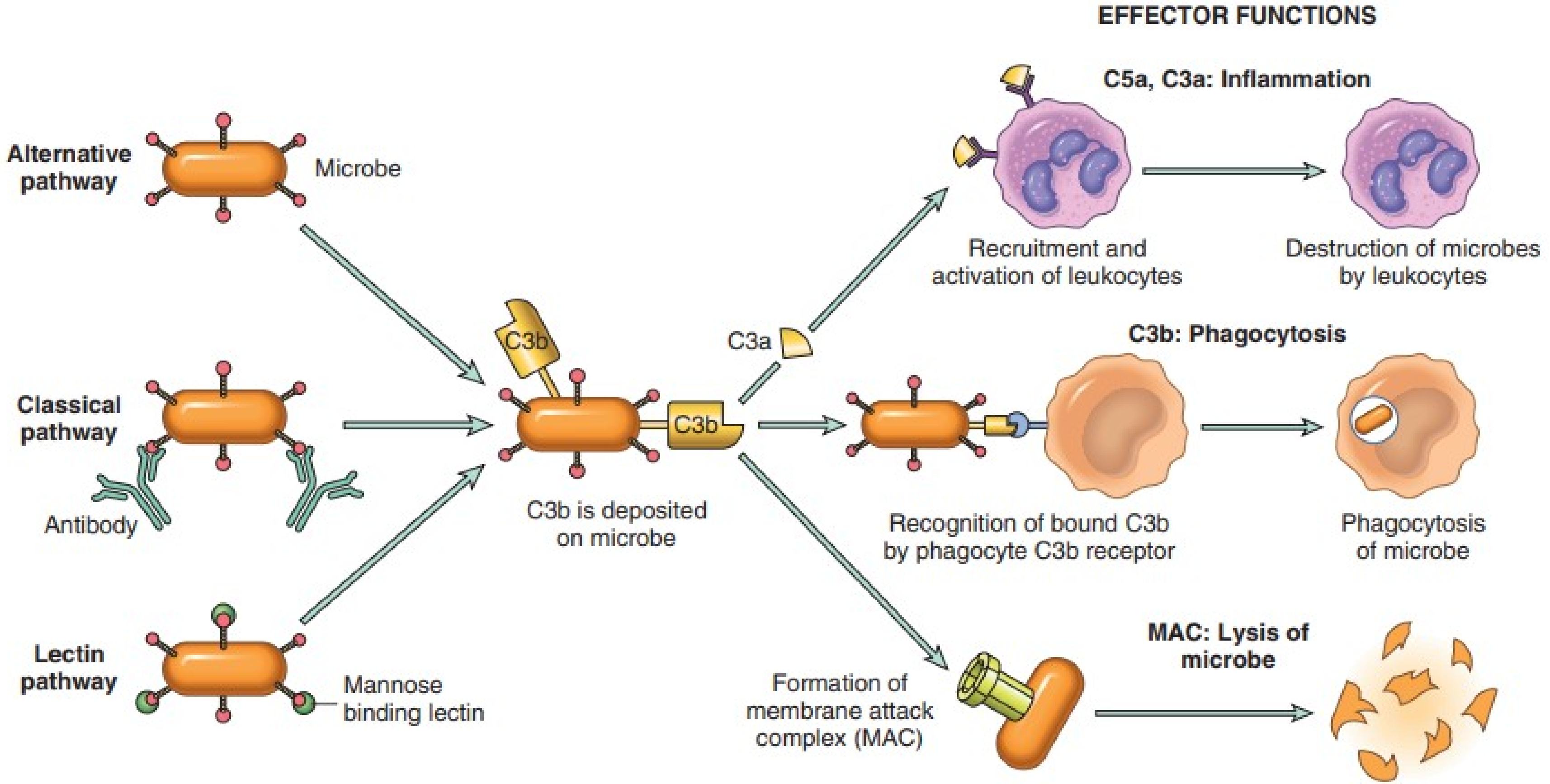

Fig. 3.11 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

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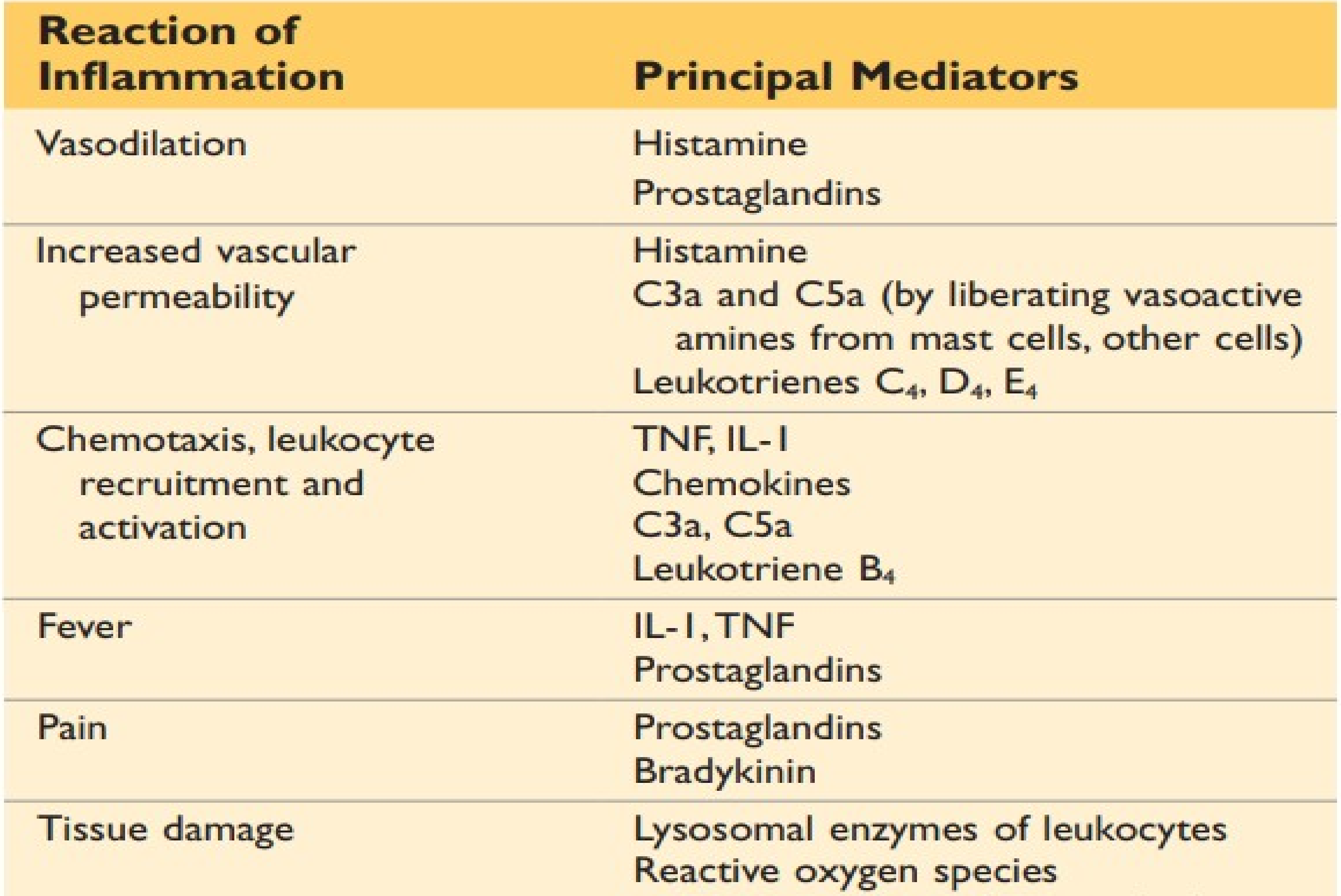

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Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

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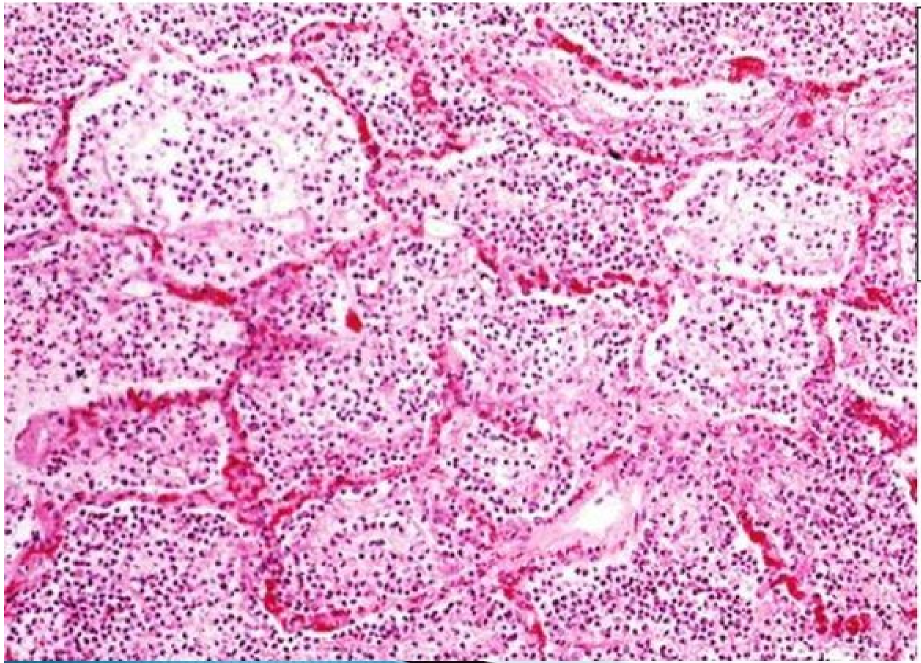
Morphologic Patterns of Acute Inflammation

SEROUS INFLAMMATION

- marked by the outpouring of a thin fluid
- The skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid

2-Fibrinous inflammation

Lung alveoli in lobar pneumonia.

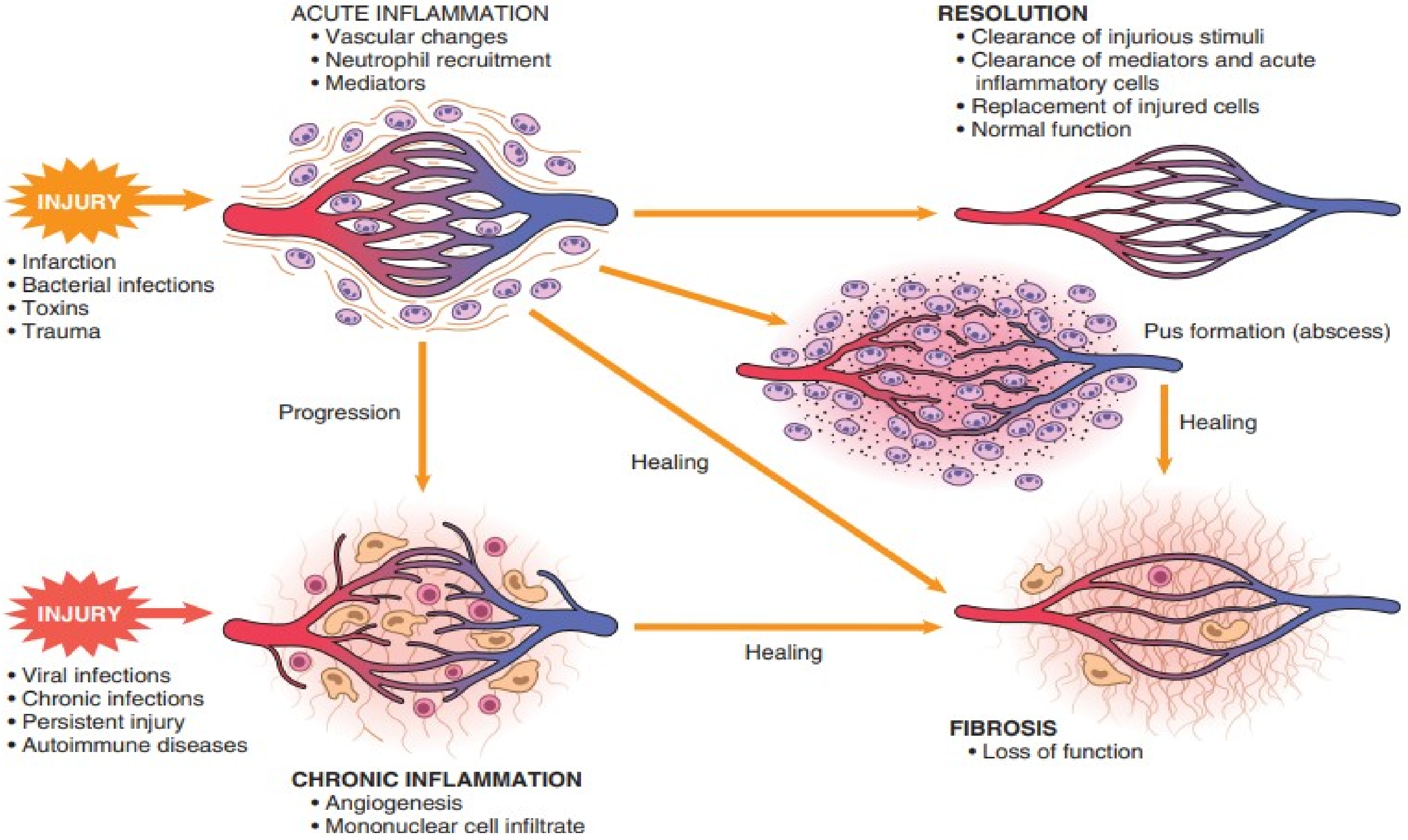


Microscopically:
fibrin threads +
Inflammatory cells

Suppurative inflammation

- Phlegmon- diffuse unbounded purulent inflammation. Types: soft and dense.
- Abscess- local purulent inflammation with necrosis and formation of cavity.
- Empyema- appearance of pus in serosal cavities or organs with cavity.
- Furuncle- purulent inflammation of hair follicle.
- Carbuncle- formation of several closely disposed furuncles with necrotic centre.

OUTCOMES OF ACUTE INFLAMMATION



chronic inflammation is characterized by:

1. Infiltration with mononuclear cells including macrophages, lymphocytes, and plasma cells.
2. Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.
3. Attempts at healing by fibrosis of the damaged tissue, achieved by proliferation of small blood vessels (angiogenesis) & fibroblasts.

Morphological Features of Chronic Inflammation

- **Macrophages**
  - Scattered all over (microglia, Kupffer cells, sinus histiocytes, alveolar macrophages, etc.
  - Circulate as monocytes and reach site of injury within 24 – 48 hrs and transform
  - Become activated by T cell-derived cytokines, endotoxins, and other products of inflammation

Chronic inflammation

- It is the inflammation of **prolong duration** (weeks or months).
- It is occurred as:
- Following acute inflammation.
- Occurs, incidentally as active inflammation.
- With tissue destruction.

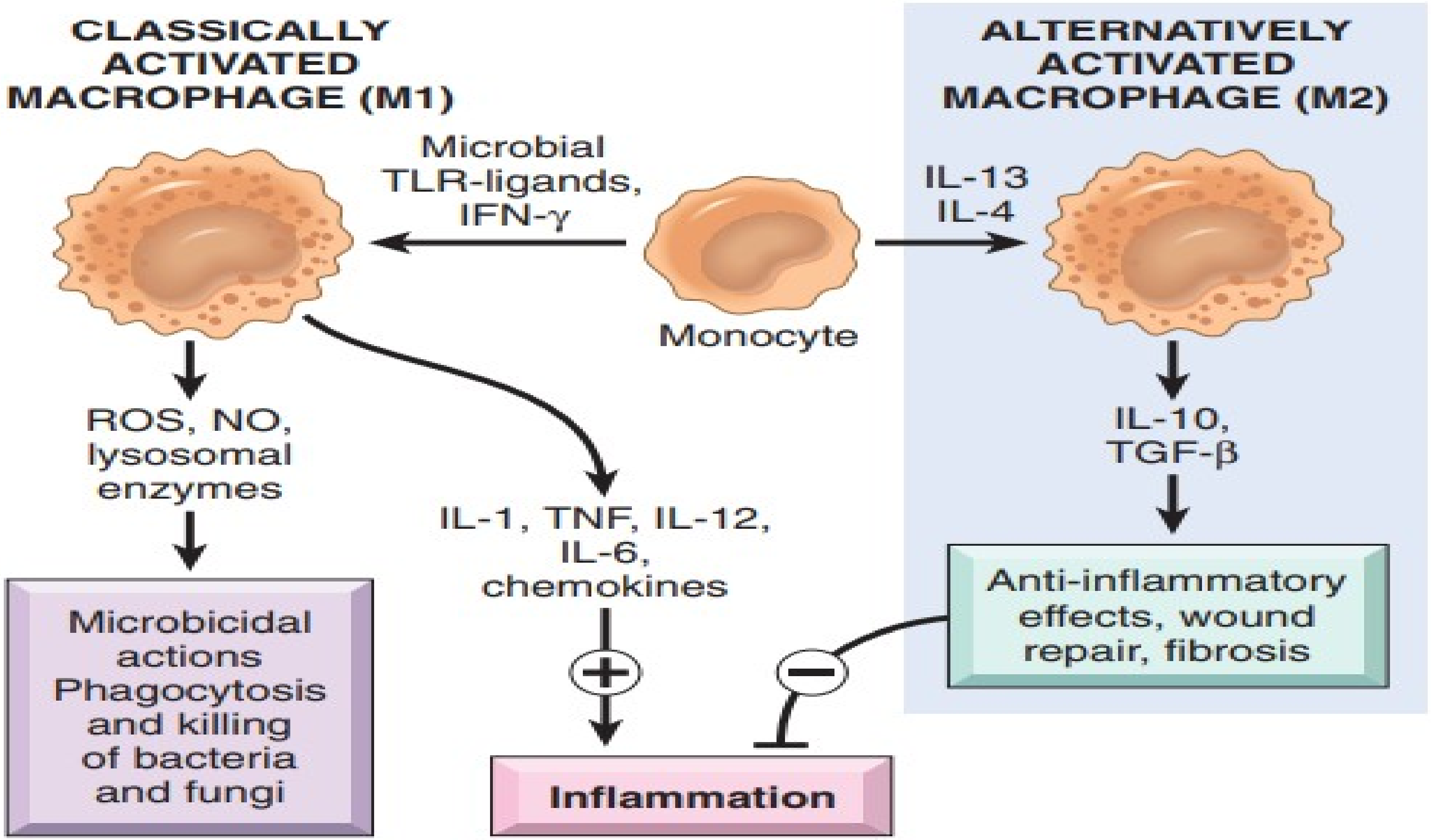
  With repair process.

Features of Chronic Inflammation

1. Infiltration with mononuclear cells, macrophages, lymphocytes, and plasma cells.

2. Tissue destruction by inflammatory cells.

3. Attempts at healing by connective tissue replacement of damaged tissue, angiogenesis (proliferation of small blood vessels) and fibrosis



CLASSICALLY ACTIVATED MACROPHAGE (M1)

Microbial TLR-ligands, IFN-γ

Monocyte

IL-13
IL-4

ALTERNATIVELY ACTIVATED MACROPHAGE (M2)

ROS, NO, lysosomal enzymes

Microbicidal actions
Phagocytosis and killing of bacteria and fungi

IL-1, TNF, IL-12, IL-6, chemokines

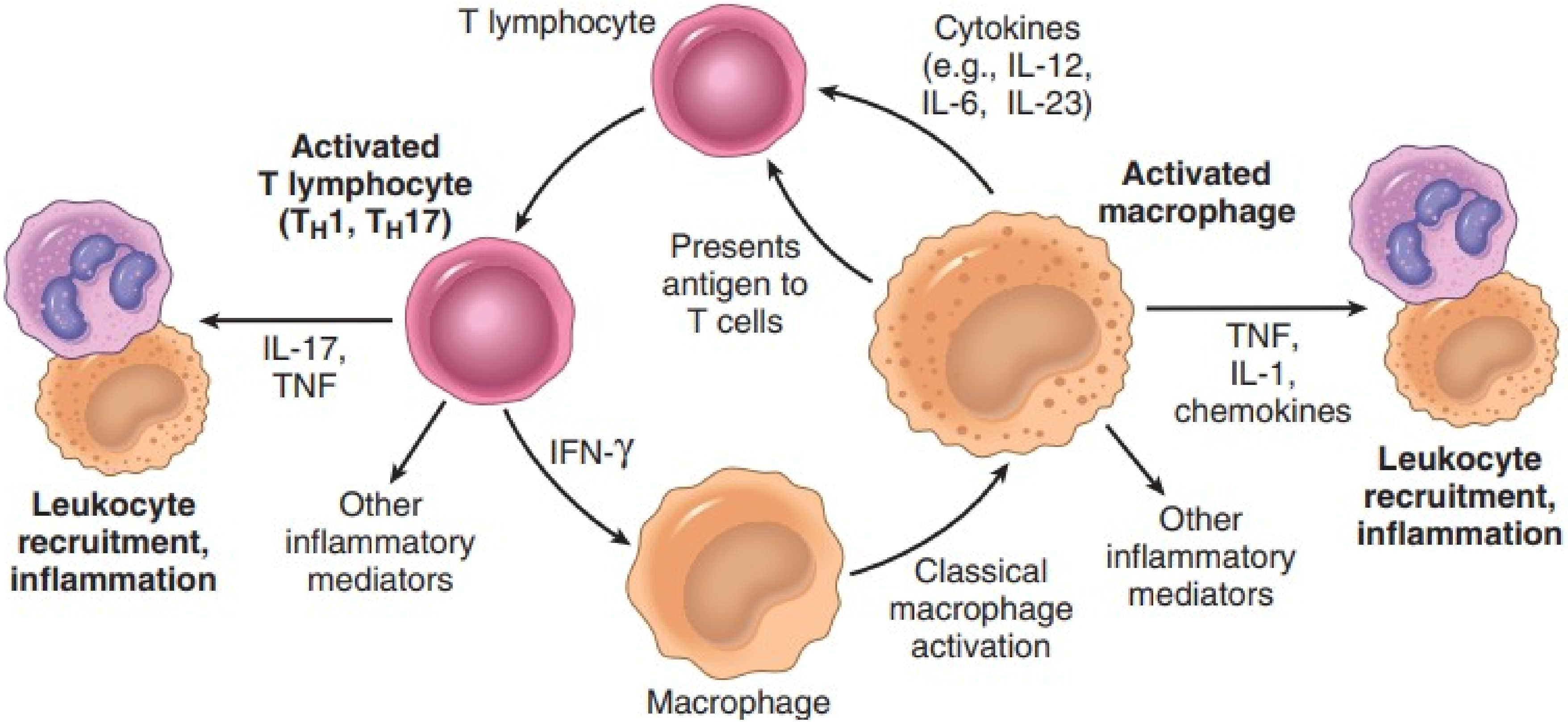
+

Inflammation

−

IL-10, TGF-β

Anti-inflammatory effects, wound repair, fibrosis

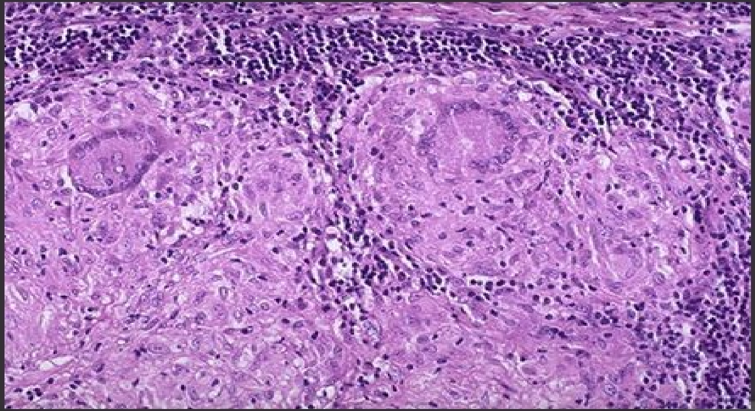

T lymphocyte
Cytokines (e.g., IL-12, IL-6, IL-23)
Activated T lymphocyte (T_H1, T_H17)
Activated macrophage
Presents antigen to T cells
IL-17, TNF
TNF, IL-1, chemokines
Leukocyte recruitment, inflammation
Other inflammatory mediators
IFN-γ
Leukocyte recruitment, inflammation
Other inflammatory mediators
Classical macrophage activation
Macrophage

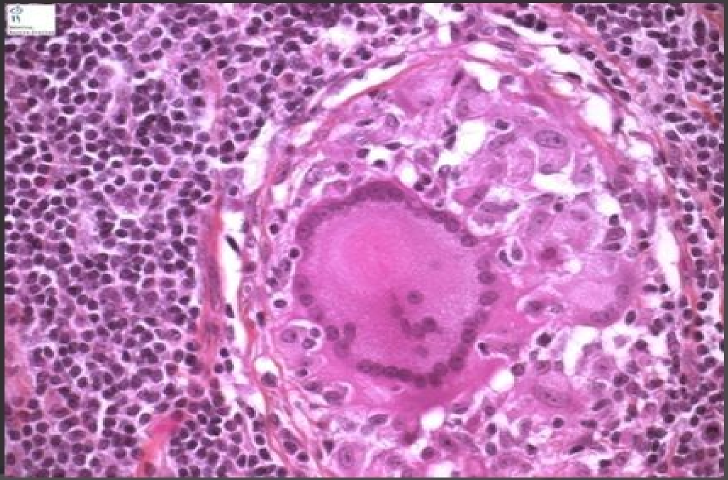
Other cells involved in chronic inflammation

- **Plasma cells:**
  - Differentiated antibody-producing B lymphocytes. Implies considerable chronicity.
- **Eosinophils:**
  - Allergic reactions, parasitic infestations, some tumours.
- **Fibroblasts / Myofibroblasts:**
  - Recruited by macrophages; make collagen. See next lecture.

Granulomatous inflammation

- Granuloma = Nodular collection of *epithelioid macrophages* surrounded by a rim of lymphocytes
- *Epitheloid macrophages*: activated macrophages have squamous cell-like appearance



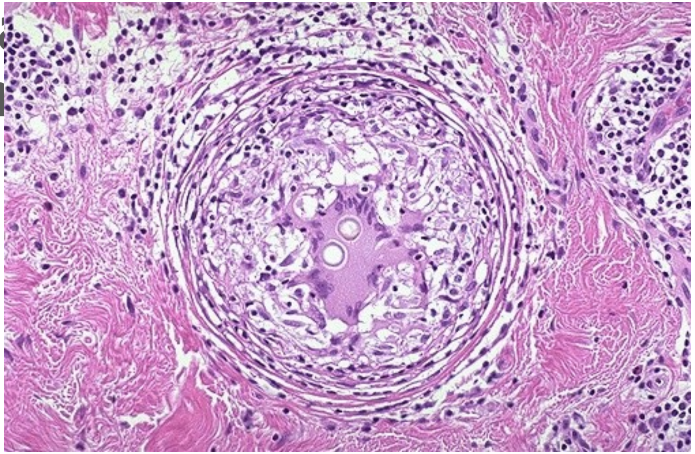


Granulomatous inflammation

- Epithelioid cells fuse to form giant cells containing 20 or more nuclei.
- The nuclei arranged either peripherally (**Langhans-type giant cell**) or
- haphazardly (**foreign body-type giant cell).**
- These giant cells can be found either at the periphery or the center of the granuloma.

Immune granulomas are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response. This type of immune response produces granulomas usually when the inciting agent cannot be readily eliminated, such as a persistent microbe or a self antigen. In such responses, macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetua

and IFN-γ, which activates the m



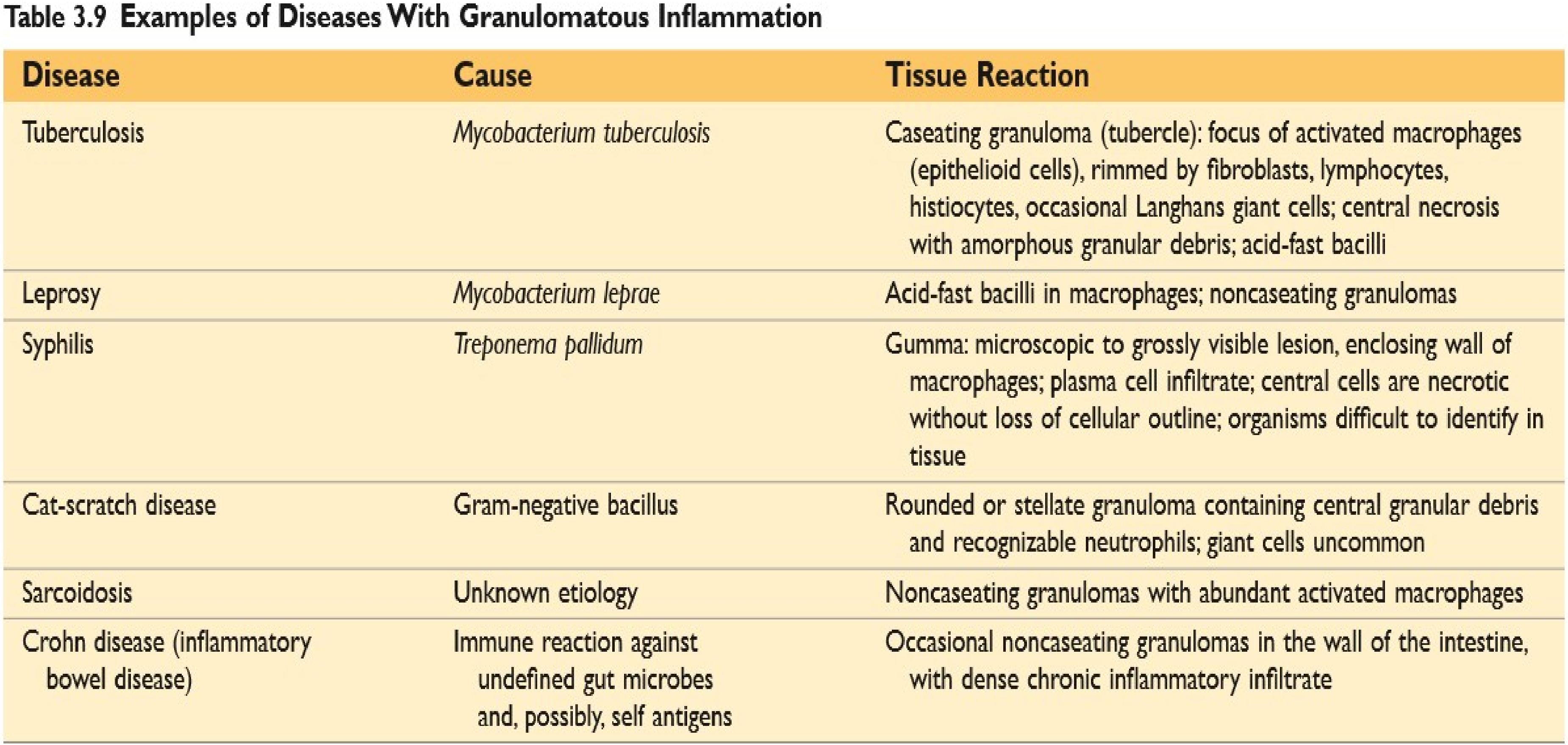


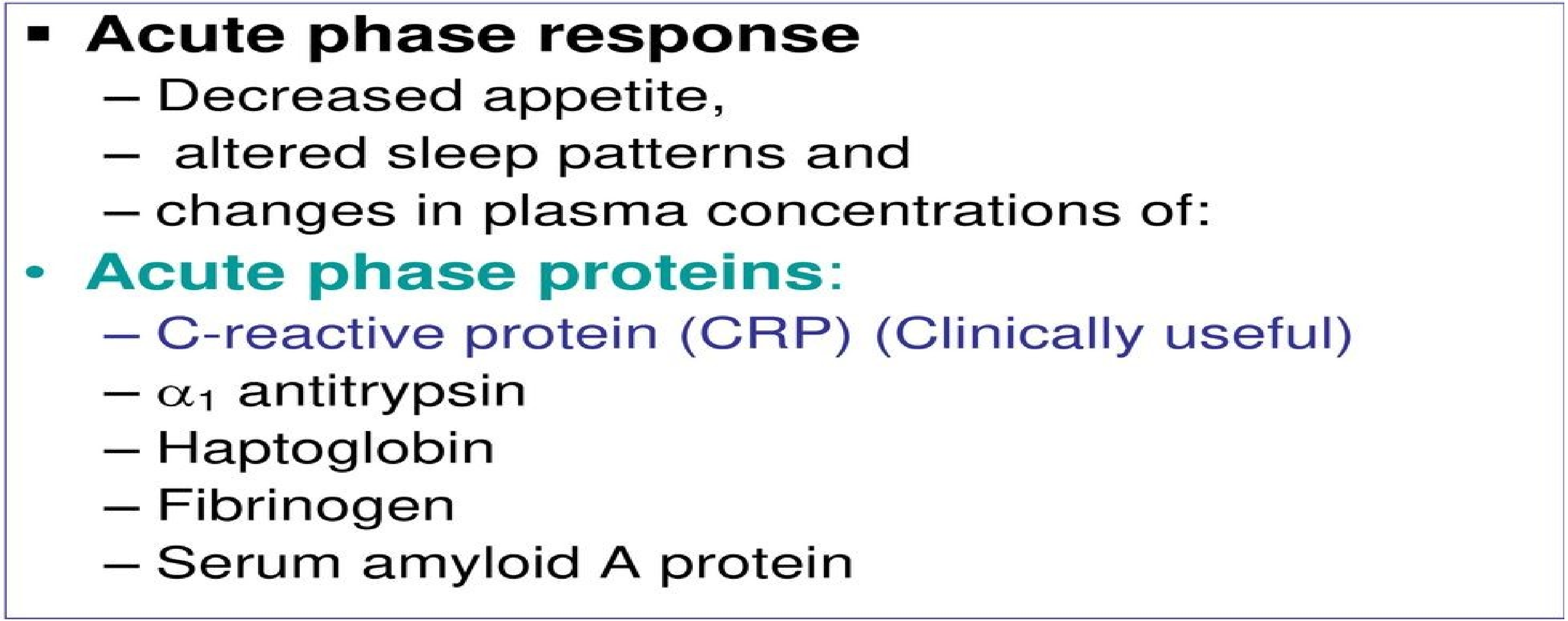
Table 3.9 **Examples of Diseases With Granulomatous Inflammation**

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Fever**
  - ‘Endogenous pyrogens’ produced: IL1 and TNFα
  - IL1 - prostaglandins in hypothalamus
    hence aspirin etc. reduce fever
- **Leukocytosis**
  - IL1 and TNFα produce an accelerated release from marrow
  - Macrophages, T lymphocytes produce colony-stimulating factors
  - Bacterial infections - neutrophils, viral - lymphocytes
  - Clinically useful

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION



- **Acute phase response**
  - Decreased appetite,
  - altered sleep patterns and
  - changes in plasma concentrations of:
- **Acute phase proteins:**
  - C-reactive protein (CRP) (Clinically useful)
  - α_1 antitrypsin
  - Haptoglobin
  - Fibrinogen
  - Serum amyloid A protein

Decreased iron,increased hepcidin

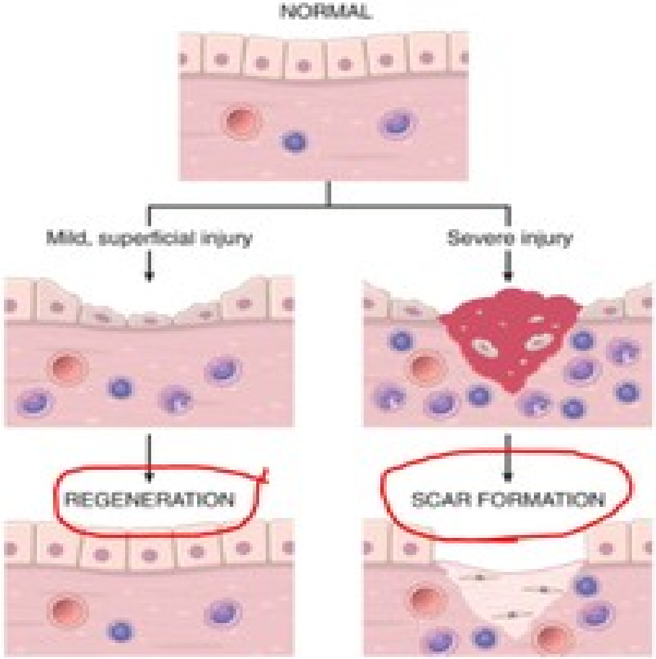
Acute phase reactants	More FFiSHH Pee in the C (sea).
POSITIVE (UPREGULATED)	
Ferritin	Binds and sequesters iron to inhibit microbial iron scavenging.
Fibrinogen	Coagulation factor; promotes endothelial repair; correlates with ESR.
Serum amyloid A	Prolonged elevation can lead to amyloidosis.
Hepcidin	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
Haptoglobin	Binds extracellular hemoglobin, protects against oxidative stress.
Procalcitonin	Rises in bacterial infections.
C-reactive protein	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.

Tissue Repair/Healing

- **Regeneration:** is complete restitution of lost tissue components identical to those removed or killed by proliferation of residual (uninjured) cells and maturation of tissue stem cells.

- **Connective tissue deposition (scar formation):** If the injured tissues are incapable of regeneration, or if the the tissue is severely damaged, repair occurs by the deposition of connective tissue.

Repair



tissues are able to replace the damaged components essentially return to a normal state;

Connective tissue deposition

Cell and Tissue Regeneration

- In some tissues (sometimes called labile tissues), cells are constantly being lost and must be continually replaced by new cells that are derived from tissue stem cells and rapidly proliferating immature progenitors. These types of tissues include hematopoietic cells in the bone marrow and many surface epithelia, such as the basal layers of the squamous epithelia of the skin, oral cavity, vagina, and cervix; the cuboidal epithelia of the ducts draining exocrine organs

- **Other tissues (called stable tissues) are made up of cells that are normally in the G0 stage of the cell cycle and hence not proliferating, but they are capable of dividing in response to injury or loss of tissue mass. These tissues include the parenchyma of most solid organs, such as liver, kidney, and pancreas.**

- Some tissues (called permanent tissues) consist of terminally differentiated non-proliferative cells, such as the majority of neurons and cardiac muscle cells. Injury to these tissues is irreversible and results in a scar, because the cells cannot regenerate

Tissue repair

Factors That Impair Wound Healing:

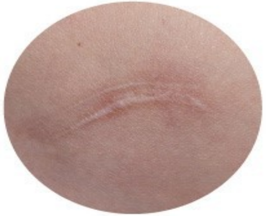
1. Malnutrition
2. Poor blood flow and hypoxia
3. Impaired immune response (immunosuppressive drugs, diseases affecting immune function such as HIV and diabetes)
4. Infection of wound
5. Foreign particles in the wound
6. Old age (decreased immune activity, poor circulation, poor nutrition)

Repair & Regeneration

- **Labile cells**: continue to proliferate throughout life : squamous, columnar, transitional epithelia; hematopoitic and lymphoid tissues
- **Stable cells:** retain the capacity of proliferation but they don’t replicate normally: parenchymal cells of all glandular organs & mesenchymal cells
- **Permanent cells:** cannot reproduce themselves after birth: neurons, cardiac muscle cells

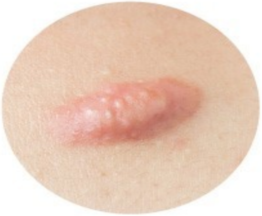
Steps in Scar Formation

- Repair by connective tissue deposition consists of sequential processes that follow tissue injury and the inflammatory response.
- **Angiogenesis** is the formation of new blood vessels, which supply nutrients and oxygen needed to support the repair process.
- Newly formed vessels are leaky because of incomplete interendothelial junctions and because VEGF, the growth factor that drives angiogenesis, increases vascular permeability.
- This leakiness accounts in part for the edema that may persist in healing wounds long after the acute inflammatory response has resolved.
- **Formation of granulation tissue.** Migration and proliferation of fibroblasts and deposition of loose connective tissue, together with the vessels and interspersed leukocytes, form *granulation tissue*.
- The **term *granulation tissue*** derives from its pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound.
- Its **histologic appearance** is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries (angiogenesis), in a loose extracellular matrix, often with admixed inflammatory cells, mainly macrophages. Granulation tissue progressively invades the site of injury; the amount of granulation tissue that is formed depends on the size of the tissue deficit created by the wound and the intensity of inflammation.



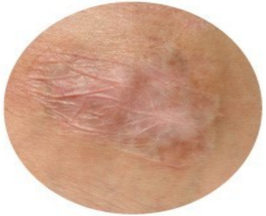
Hypertrophic scars

excessive collagen deposits appear raised, but not to the degree observed with keloids



Keloid scars

can appear as a firm, rubbery lesion or shiny, fibrous nodules



Contracture scars:

are characterized by extremely tight skin that can restrict your ability to move.

Wound contraction is an important part of the normal healing process. An exaggeration of this process gives rise to contracture and results in deformities of the wound and the surrounding tissues. Contractures are particularly prone to develop on the palms, the soles, and the anterior aspect of the thorax. Contractures are commonly seen after serious burns and can compromise the movement of joints.

Wound healing

1. Primary union (healing by 1st intention)
   - clean surgical incision
   - no significant bacterial contamination
   - minimal loss of tissue
   - clot, scab formation

24 hr.: neutrophils, mitotic activity of basal layer, thin epithelial layer ↑

day 3: macrophages, granulation tissue

day 5: collagen bridges the incision, epidermis thickens

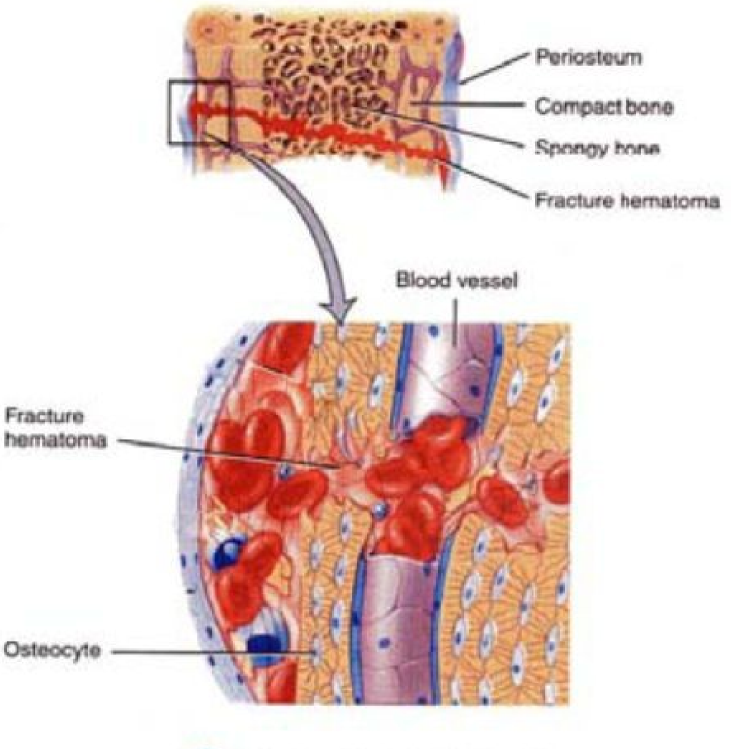
2nd week: continued collagen and fibroblasts, blanching

End of 1st month: scar (cellular connective tissue, intact epidermis, lost appendages).

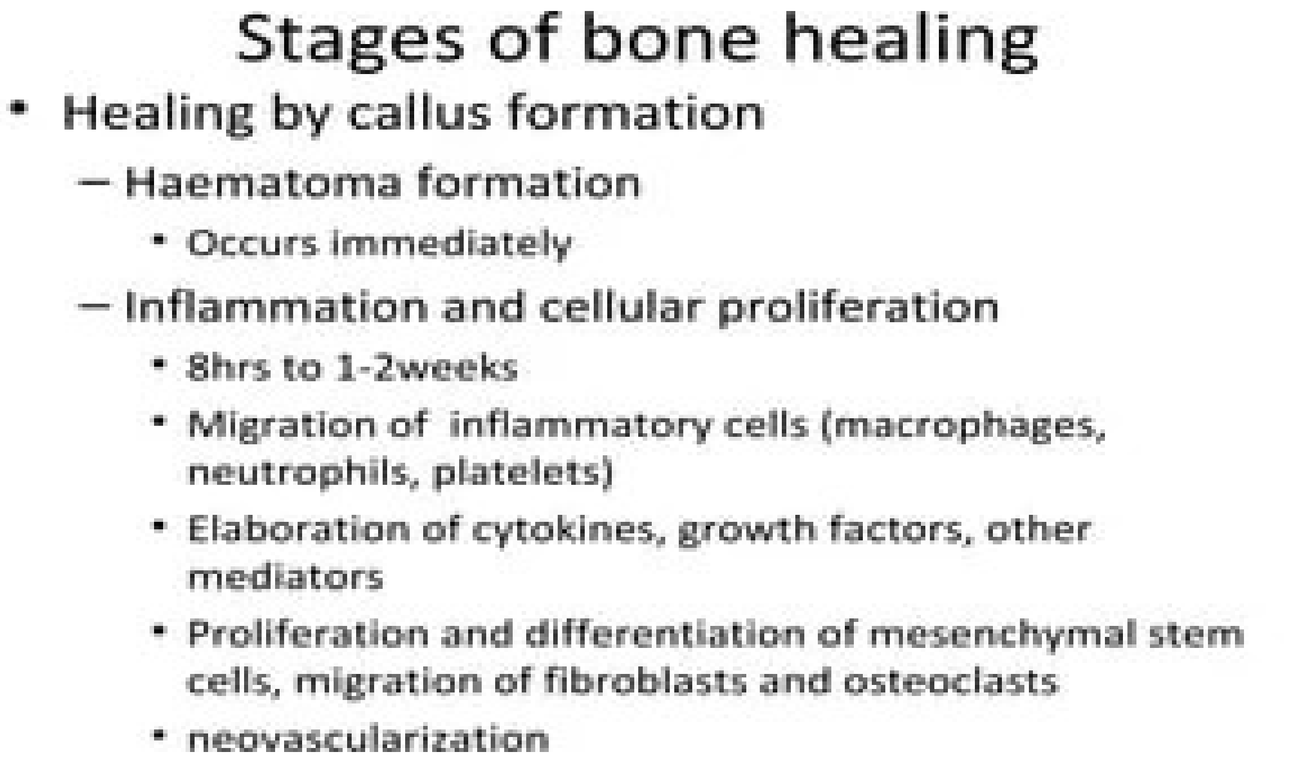
Bone Healing

1. Fracture hematoma

- – blood from broken vessels forms a clot.
- – 6-8 hours after injury
- – swelling and inflammation to dead bone cells at fracture site



① Formation of fracture hematoma



Stages of bone healing

- Healing by callus formation
  - Haematoma formation
    - Occurs immediately
  - Inflammation and cellular proliferation
    - 8hrs to 1-2weeks
    - Migration of inflammatory cells (macrophages, neutrophils, platelets)
    - Elaboration of cytokines, growth factors, other mediators
    - Proliferation and differentiation of mesenchymal stem cells, migration of fibroblasts and osteoclasts
    - neovascularization

Vascular endothelial growth factor (VEGF) participates in Angiogenesis.